

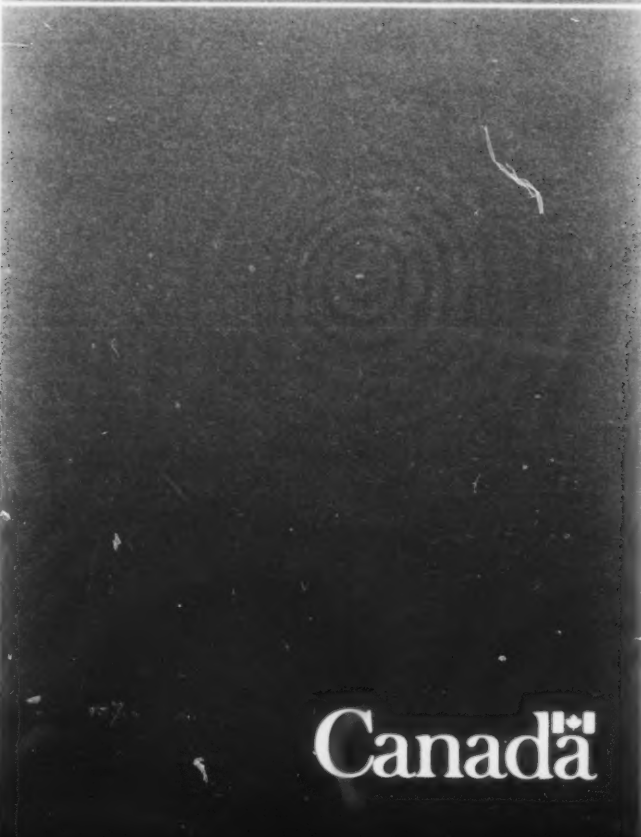


Report Rapport



Atomic Energy
Control Board

Commission de contrôle
de l'énergie atomique



Canada



Atomic Energy
Control Board

P.O. Box 1046
Ottawa, Canada
K1P 5S9

Commission de contrôle
de l'énergie atomique

C.P. 1046
Ottawa, Canada
K1P 5S9

INFO-0424

**OCCUPATIONAL EXPOSURE OF FATHERS
TO IONIZING RADIATION AND THE RISK
OF LEUKAEMIA IN OFFSPRING —
A CASE-CONTROL STUDY**

(AECB Project No. 7.157.1)

by

J.R. McLaughlin^{1,2}

T.W. Anderson³

E.A. Clarke^{1,2}

W. King¹

A research report prepared for
the Atomic Energy Control Board
Ottawa, Canada

¹The Ontario Cancer Treatment
and Research Foundation

²The University of Toronto

³University of British Columbia

August 1992

Canada

Research report

OCCUPATIONAL EXPOSURE OF FATHERS TO IONIZING RADIATION AND THE RISK OF LEUKAEMIA IN OFFSPRING — A CASE-CONTROL STUDY

A report prepared by Dr. J.R. McLaughlin, Dr. E.A. Clarke and Mr. W. King of the Division of Epidemiology and Statistics of the Ontario Cancer Treatment and Research Foundation, and Dr. T.W. Anderson of the University of British Columbia, under contract to the Atomic Energy Control Board.

SUMMARY

An epidemiologic study was performed to determine whether there was an association between childhood leukaemia and the occupational exposure of fathers to ionizing radiation prior to the time of the child's conception. The study focused on the effect of exposures received during employment in the nuclear industry, particularly in the period before a child's conception.

The study employed a case-control design, whereby children with cancer ("cases") and children who did not develop cancer ("controls") were compared with respect to their prior exposure history. The case series consisted of children (ages 0-14 years) who died from or were diagnosed with leukaemia and were born to mothers who, at the time of the child's birth, resided in the vicinity of an operating nuclear facility in Ontario. Cases occurring from 1950 to 1988 were identified from the Ontario Cancer Registry. The residence of parents at the time of each case's birth was determined from birth certificates.

Eight controls per case were identified from birth certificates. Control children were those who had not developed leukaemia by the time the index case was diagnosed and were matched to a case according to date of birth and mother's residence at the time of birth. Six control children were ineligible because they died prior to the development of the associated case's leukaemia. Thus, there were 112 cases and 890 controls included in the analysis, for a total of 1002 study subjects.

Data pertaining to occupational radiation exposure of the 1002 fathers were obtained by a computerized record linkage with the Canadian National Dose Registry (NDR) and subsequent examination of employer records. Links to the NDR were identified for 95 fathers: of these, 52 were reactor workers, 31 were uranium miners, 10 worked in other industries, one was a medical worker and one had an unknown job class.

For each father identified in the NDR, radiation doses were obtained regarding whole body external dose in millisieverts (mSv), which was largely due to gamma radiation and, in addition, (a) tritium dose (in mSv), which is the most common type of whole body internal exposure received by Canadian nuclear reactor workers, and (b) for uranium miners, internal exposures to the lungs due to radon and radon progeny (in working level months). Total whole body dose was calculated for each father by summing the external whole body dose and tritium dose. Radiation exposures were estimated for four periods: (a) over the father's lifetime, prior to the

child's conception, (b) during the six-month period prior to the child's conception, (c) during the three-month period prior to the child's conception, and (d) over the father's lifetime, ending in the month of the child's diagnosis. In order to permit the accurate estimate of radiation dose for periods of specific interest, dose data in as much detail as possible were obtained from the NDR and employers.

Several factors that could have potentially affected the quality of the exposure and the outcome data were evaluated and found not to have diminished the validity of the study results. For example, leukaemia diagnoses were reviewed, the procedures used for linkage with the NDR were formally tested and the radiation doses obtained from the NDR were compared with employer records.

The statistical analysis included the calculation of odds ratios (OR) by means of conditional logistic regression analysis. As an estimate of relative risk, an odds ratio of 1.0 would indicate that leukaemia risk in children of exposed fathers was equal to that among children of fathers who were not exposed. An odds ratio greater than 1.0 would indicate that the risk of leukaemia was greater among the children of exposed than unexposed fathers. Confidence intervals (CI) and tests of statistical significance were also computed.

The primary focus of this study was on the effects of radiation exposures occurring prior to a child's conception. There was no evidence of an elevated leukaemia risk in relation to any exposure period (lifetime, six months or three months prior to conception) or exposure type (total, external or internal dose). For example, the odds ratio for any exposure to radiation (total dose > 0.0 mSv) during a father's lifetime prior to conception was 0.87 (95% confidence interval of 0.32 to 2.34), which was based on the exposure of fathers of six cases and 53 controls. For any whole body exposure to radiation during the six-month period prior to conception, the odds ratio was 0.96 (95% CI = 0.34-2.77), based on the exposure of fathers of five cases and 41 controls. Also, there was no apparent gradient of effect with increasing radiation dose. For example, the odds ratio for total whole body doses before conception were 1.0, 0.80 and 1.09 for doses of 0.0, 0.1-49 and 50 or more mSv, respectively, which indicated that with increasing dose there was not a corresponding increase in risk. Paternal exposures up to the time of a case's diagnosis or death were also considered and found not to be associated with the occurrence of childhood leukaemia.

The radiation doses that were reported by Gardner et al.^{1,2} to be most strongly associated with leukaemia risk were specifically considered in this study. None of the cases in this study had fathers with either a lifetime preconception dose of 100 mSv or greater (whereas five controls fell into this category), or a six-month preconception dose of 10 mSv or more (compared with nine controls). The prevalences of exposure to these radiation doses were similar among the fathers of controls in this study and in the study by Gardner et al.^{1,2} The fact that relatively high preconception doses occurred among the fathers of controls but not cases emphasized that the dose-response relationship reported by Gardner et al.^{1,2} did not occur in this study.

The largest, but also the least stable, relative risk estimates seen in this study referred to uranium miners, with an odds ratio of 7.27 (95% CI = 0.59-88.7). In the region surrounding the Elliot Lake uranium mines, only five cases of childhood leukaemia occurred between 1954

and 1988, so that all the information about uranium mining arose from five matched sets of cases and controls. Given that (a) statistical significance was not achieved, (b) the majority of radon dose would be to the lungs rather than other tissues, and (c) a previous ecologic study found that the mining region did not have an excess of childhood leukaemia³, it is concluded that the observations pertaining to uranium miners were a chance finding due to random variation associated with small numbers.

The analysis of covariables that were available from birth certificates showed that the risk of childhood leukaemia (a) was, as expected, slightly greater for boys than for girls, (b) increased slightly in association with increasing birth weight, (c) decreased slightly with higher birth orders, and (d) decreased slightly with increasing maternal age. Multivariable analyses that controlled for the effects of these covariables did not alter conclusions regarding the effects of radiation that were drawn on the basis of simple univariable analyses.

It is concluded that there was no association between childhood leukaemia and the occupational exposure of fathers to ionizing radiation prior to the time of conception. This conclusion applies in particular to radiation exposures arising from employment in the nuclear industry in Ontario. No association was detected for external whole body dose, tritium dose or radon exposures, or for any of the preconception or prediagnosis periods of exposure. Odds ratios were close to 1.0 for all radiation dose categories and occupations except for uranium mining, which had a larger, but not statistically significant odds ratio.

The findings of this study in Ontario are not consistent with the hypothesis that childhood leukaemia is associated with the occupational exposure of fathers to radiation prior to conception, as was found in the case-control study at Sellafield in the United Kingdom by Gardner et al.² The results from Ontario provide evidence against the existence of such an association for exposures to either whole body external radiation or tritium.

RÉSUMÉ

Le présent rapport rend compte de l'étude épidémiologique qui a été entreprise pour déterminer s'il existait un lien entre la leucémie infantile et les expositions professionnelles du père aux rayonnements ionisants dans l'industrie nucléaire, notamment au cours de la période précédant la conception de l'enfant.

L'étude est du type cas-témoins, où l'on compare des enfants atteints de cancer («cas») à des enfants non atteints («témoins») par rapport à leurs antécédents d'exposition. Le groupe des cas comprenait des enfants (de 0 à 14 ans) atteints de leucémie ou morts de leucémie et nés de mères qui, à la naissance de l'enfant, résidaient dans les environs d'une centrale nucléaire en exploitation en Ontario. Les cas survenus entre 1950 et 1988 ont été relevés dans le Registre de cancer de l'Ontario. Le lieu de résidence des parents à la naissance de chacun des enfants a été établi d'après les certificats de naissance.

Huit témoins par cas ont été relevés d'après les certificats de naissance. Les enfants témoins sont ceux qui n'avaient pas la leucémie au moment où le cas de référence a été diagnostiqué et ils ont été associés à un cas en fonction de la date de naissance et du lieu de résidence de la mère au

moment de la naissance. Six témoins n'ont pas été retenus parce qu'ils étaient morts avant l'apparition de la leucémie chez le cas associé. En tout, l'analyse portait sur 112 cas et 890 témoins, soit un total de 1002 sujets.

Les données se rapportant à l'exposition professionnelle à des rayonnements des 1002 pères ont été obtenues à la suite du chaînage des fichiers informatiques avec le Fichier dosimétrique national et de l'examen subséquent des dossiers des employeurs. Des liens ont été établis avec le Fichier dosimétrique national dans le cas de 95 pères. De ce nombre, 52 travaillaient dans des centrales, 31 dans des mines d'uranium, 10 dans d'autres industries et l'un était travailleur médical. La catégorie d'emploi de l'un des travailleurs était inconnue.

Pour chacun des pères relevés dans le Fichier dosimétrique national, on a obtenu les doses de rayonnement du corps entier en millisieverts (mSv), attribuables en grande partie à des rayonnements gamma, ainsi que : a) la dose de tritium (en millisieverts), qui est le type le plus courant d'exposition interne des travailleurs des centrales nucléaires canadiennes et b) les doses d'exposition des poumons des mineurs d'uranium, attribuables au radon et à ses produits de filiation (en unités alpha-mois). On a calculé la dose du corps entier de chacun des pères en additionnant la dose externe du corps entier et la dose de tritium. Les expositions aux rayonnements ont été estimées pour quatre périodes : a) la vie du père jusqu'à la conception de l'enfant; b) le semestre précédant la conception de l'enfant; c) le trimestre précédant la conception de l'enfant et d) la vie du père jusqu'au mois de diagnostic de la maladie chez l'enfant. Afin de parvenir à une estimation précise de la dose de rayonnements au cours des périodes d'intérêt particulier, on a obtenu du Fichier dosimétrique national et des employeurs les données le plus détaillées possible sur la dose.

On a évalué plusieurs facteurs qui auraient pu affecter la qualité de l'exposition et les données résultantes et constaté qu'ils n'avaient pas diminué la validité des résultats de l'étude. Par exemple, on a examiné les diagnostics de leucémie, mis à l'épreuve les procédures de couplage avec le Fichier dosimétrique national et comparé les doses de rayonnement obtenues du Fichier avec les dossiers des employeurs.

L'analyse statistique comprenait le calcul du risque relatif à l'aide d'analyses de régression logistique conditionnelle. En tant qu'estimation d'un risque relatif, un facteur de 1,0 indiquerait que le risque de leucémie chez les enfants de pères ayant été exposés aux rayonnements était égal à celui des enfants de pères non exposés. Un facteur supérieur à 1,0 indiquerait que le risque de leucémie était plus élevé chez les enfants de pères ayant été exposés à des rayonnements. On a également calculé les intervalles de confiance et les indices de signification statistique.

L'étude a porté principalement sur les effets de l'exposition aux rayonnements avant la conception d'un enfant. Il n'y avait pas de preuve de risque élevé de leucémie par rapport à une période (la vie entière, le semestre ou le trimestre avant la conception) ou à un type d'exposition (dose du corps entier, externe ou interne). Par exemple, le facteur de risque pour toute exposition à des rayonnements (dose totale supérieure à 0,0 mSv) au cours de la vie d'un père avant la conception était de 0,87 (intervalle de confiance de 95 pour 100 entre 0,32 et 2,34), d'après l'exposition des pères de six cas et de 53 témoins. Le facteur de risque était de 0,96

(intervalle de confiance de 95 pour 100 entre 0,34 et 2,77) dans le cas de toute exposition du corps entier au cours des six mois précédant la conception, d'après l'exposition des pères de cinq cas et de 41 témoins. De plus, il n'y avait pas de gradient d'effet apparent avec l'élévation de la dose de rayonnement. Par exemple, les facteurs de risque pour les doses du corps entier avant la conception étaient de 1,0, 0,80 et 1,09 pour des doses respectives de 0,0 mSv, de 0,1 à 49 mSv et de 50 mSv et plus, ce qui indique qu'il n'y a pas d'augmentation du risque correspondant à l'accroissement de la dose. On a tenu compte de l'exposition du père jusqu'au moment du diagnostic de la maladie ou jusqu'au décès de l'enfant et on a constaté qu'il n'y avait pas de lien avec l'occurrence des cas de leucémie infantile.

Lors de l'étude, on a tenu compte plus particulièrement du fait que les doses de rayonnement rapportées par Gardner et al.^{1,2} étaient fortement associées au risque de leucémie. Aucun des cas de la présente étude n'était relié à un père ayant eu une dose de 100 mSv ou plus pour l'ensemble de sa vie professionnelle jusqu'au moment de la conception (alors que cinq témoins entraient dans cette catégorie) ni une dose de 10 mSv ou plus au cours des six mois précédant la conception (comparativement à neuf témoins). Ces doses de rayonnement étaient similaires chez les pères des témoins de l'étude et dans l'étude de Gardner et al.^{1,2}. Le fait que des doses relativement élevées avant la conception aient été enregistrées chez les pères du groupe témoin mais non chez les pères des cas montre clairement que la relation dose-réponse rapporté par Gardner et al.^{1,2} ne s'est pas manifestée dans la présente étude.

Les estimations de risque relatif les plus importantes mais aussi les moins stables de l'étude font référence aux mineurs d'uranium pour qui le facteur de risque est de 7,27 (intervalle de confiance de 95 pour 100 entre 0,59 et 88,7). Dans la région entourant les mines d'uranium d'Elliot Lake, on n'a relevé que cinq cas de leucémie infantile entre 1954 et 1988, de sorte que tous les renseignements relatifs aux mines d'uranium provenaient de cinq ensembles de cas et de témoins. Compte tenu : a) que les résultats ne sont pas statistiquement significatifs; b) que la plus grande partie de la dose due au radon est délivrée aux poumons plutôt qu'à d'autres tissus et c) qu'une étude écologique antérieure avait permis de constater que la région minière ne présentait pas un excédent de cas de leucémie infantile³, on en conclut que les observations se rapportant aux mineurs d'uranium résultent d'une constatation fortuite attribuable à des variations aléatoires liées aux petits nombres.

L'analyse des covariables notées sur les certificats de naissance a montré que le risque de leucémie infantile : a) était, tel que prévu, un peu plus élevé chez les garçons que chez les filles; b) s'accroissait légèrement avec l'augmentation du poids à la naissance; c) diminuait légèrement avec l'augmentation du rang de naissance dans la famille et d) diminuait légèrement avec l'augmentation de l'âge de la mère. L'analyse à variables multiples qui prend en compte les effets de ces covariables n'a pas altéré les conclusions concernant les effets des rayonnements tirées de simples analyses à variables uniques.

Les auteurs de l'étude concluent qu'il n'y avait pas d'association entre la leucémie infantile et l'exposition professionnelle des pères à des rayonnements ionisants avant la conception. Cette conclusion vise en particulier l'exposition de travailleurs du secteur nucléaire en Ontario. Aucune association n'a pu être décelée dans le cas des doses externes du corps entier, des doses de tritium ou de l'exposition au radon, ni pour aucune des périodes d'exposition antérieures à la conception.

ou au diagnostic. Le facteur de risque se rapprochait de 1,0 pour l'ensemble des catégories de dose de rayonnement et des occupations, sauf dans le cas des mineurs d'uranium qui présentaient un facteur de risque plus grand mais non significatif du point de vue statistique.

Les conclusions de cette étude pour l'Ontario ne confirment pas l'hypothèse selon laquelle la leucémie infantile est associée à l'exposition professionnelle du père à des rayonnements avant la conception de l'enfant, comme l'ont constaté Gardner et al.² dans l'étude cas-témoins à Sellafield, au Royaume-Uni. Les résultats de l'étude menée en Ontario fournissent des données qui vont à l'encontre d'une telle association dans le cas d'expositions à des rayonnements externes du corps entier ou au tritium.

DISCLAIMER

The Atomic Energy Control Board is not responsible for the accuracy of the statements made or opinions expressed in this publication and neither the Board nor the authors assume liability with respect to any damage or loss incurred as a result of the use made of the information contained in this publication.

TABLE OF CONTENTS

SUMMARY	i
DISCLAIMER	vi
LIST OF ABBREVIATIONS	ix
A. INTRODUCTION	1
B. LITERATURE REVIEW AND RELEVANCE	1
1 Ecologic Studies	1
2 Risk Factors and Analytic Studies	2
3 The Relevance of the Ontario Setting	4
C. OBJECTIVE	4
D. METHODS	4
1 Design	4
2 Case Selection	5
3 Case Confirmation	6
4 Case Description	7
5 Control Selection	8
6 Data Collection	10
7 Record Linkage to the NDR	10
8 Radiation Dose Data	12
8.1 Variation in Procedures Used to Estimate Radiation Dose	14
9 Covariables	14
10 Statistical Methods	15
E. RESULTS	15
F. DISCUSSION	25
1 Interpretation of the Results	25
2 Validity Considerations	28
2.1 Potential Biases	28
2.2 Uncertainty in Measuring Radiation Dose	29
2.3 Misclassification of Linkage Status	30
2.4 Detection of Non-nuclear Workers	30
2.5 Uncertain Leukaemia Diagnoses	31
2.6 Emigration from Ontario	31
2.7 Summary of Validity Considerations	32

3	Statistical Power of the Study	32
4	Comparison with Previous Studies	33
5	Strengths and Limitations	34
6	Conclusions	35
7	Recommendations	35

REFERENCES	36
-----------------------------	----

ACKNOWLEDGMENTS	42
----------------------------------	----

GLOSSARY	43
---------------------------	----

APPENDICES:

Maps of "Worker Areas"	Appendix A
----------------------------------	------------

Procedures, Application and Evaluation of the Record Linkage to the NDR . . .	Appendix B
---	------------

Details of Variation in Procedures Used to Estimate Radiation Dose	Appendix C
--	------------

The Impact of Uncertainty in Radiation Dose Measurement	Appendix D
---	------------

LIST OF ABBREVIATIONS

AECB	The Atomic Energy Control Board
AECL	Atomic Energy Canada Ltd.
BEIR	Committee on the Biological Effects of Ionizing Radiations
CI	confidence interval
df	degrees of freedom
ICRP	International Commission on Radiological Protection
LR	likelihood ratio
NDR	National Dose Registry
OCR	Ontario Cancer Registry
O/E	ratio of the observed (O) to the expected (E) number of cancers
OR	odds ratio
p	probability

Units of radiation measurement:

MeV	million electron volts
mGy	milligray
mR	milliroentgen
mrad	millirad (a measure of absorbed dose)
mrem	millirem (a measure of dose equivalent; rad equivalent, man)
mSv	millisievert
uCi/L	microcuries per litre
WLM	working level month

A. INTRODUCTION

A case-control study was conducted in Ontario to examine whether there is an association between the occurrence of childhood leukaemia and the cumulative occupational exposure of fathers to ionizing radiation at the time of the child's conception. This report presents a review of relevant literature, followed by the objective, methods, results and discussion of the Ontario study. Details regarding methodologic and analytic issues are summarized in several appendices.

B. LITERATURE REVIEW AND RELEVANCE

The leukaemogenic effect of ionizing radiation has been demonstrated in a wide variety of settings. Studies of human populations exposed to radiation from atomic bombs,⁴ medical procedures^{5,6} and occupational sources^{7,8} have consistently detected an association between leukaemia and radiation exposure. These studies have suggested that leukaemia is the cancer that occurs with the shortest latency after exposure to ionizing radiation. Several studies have also shown that the likelihood of developing leukaemia is greatest among those who are young at the time of exposure.^{9,10,11,12,13} Childhood leukaemia is, therefore, of particular interest as an outcome in studies of radiation carcinogenesis.

Exposures to ionizing radiation can occur in several ways in the nuclear industry. Workers are routinely exposed to low levels of radiation in the mining, milling or refining of uranium, in the research and development of reactor systems, in the operation and maintenance of reactors and in the handling and storage of radioactive waste material. Low levels of radioactive emissions are also released into the environment during the routine operation of nuclear facilities. In the event of an accident, higher levels of occupational exposure and emission to the environment may occur.

B.1 Ecologic Studies

The question of whether cancer rates and, in particular, leukaemia rates are higher than expected among populations living in the vicinity of nuclear facilities has been examined in several countries. No excess of leukaemia was found in studies of facilities in France^{14,15} and the U.S.A.,^{16,17} except at Three Mile Island where there was a small excess that was within the bounds of chance variation.¹⁸ A statistically significant excess of childhood leukaemia was detected in the vicinity of German facilities.^{19,20}

Reports of several studies in the United Kingdom (U.K.) aroused worldwide interest in the question of whether cancer is associated with nuclear facilities. Significantly elevated rates of leukaemia were first reported by ecologic studies of populations residing in the vicinity of the Sellafield²¹ and Dounreay²² nuclear fuel reprocessing facilities. Subsequent studies of other facilities in the U.K. detected significant excesses of childhood leukaemia around facilities that began operation prior to 1955,²³ facilities involved in the development, manufacturing and storage of nuclear weapons,²⁴ and a single nuclear power station.²⁵

In a more detailed analysis of childhood leukaemia rates in the vicinity of the Sellafield facility, Gardner et al.^{26,27} demonstrated that the excess leukaemia mortality was restricted to children who were born in the region (5 cases were observed (O), whereas 0.53 were expected (E)). There was no leukaemia excess among children who went to school but were not born in the area (O=0, E=0.54). The fact that the excess risk was limited to a birth cohort indicated that the unknown factor responsible for the excess leukaemia probably had its effect close to the time of birth rather than later in childhood.

Following the reports of leukaemia clusters in the U.K., Clarke et al.³ performed an ecologic study of childhood leukaemia rates from 1950 to 1987 in five regions of Ontario within 25 kilometres (km) of a nuclear facility. The primary aim of the Ontario study was to determine whether the leukaemia mortality and incidence rates among children born to mothers residing in the vicinity of the nuclear facilities differed from the provincial average. This study was specifically designed to determine whether the birth cohort phenomenon identified by Gardner et al.^{26,27} was present in Ontario. Overall, the observed number of leukaemia deaths (O=54) was slightly greater than expected (E=46.1) during the period of facility operation, but the difference was within the bounds of chance variation. There was no indication of a cohort effect as seen by Gardner et al.,^{26,27} as the relative risk based on place of birth was not significantly greater than that based on place of death. In the analyses of individual facilities, confidence intervals (CI) were generally wide because of the small observed and expected numbers; however, in the vicinity of the nuclear generating stations, the observed relative excess of leukaemia (O=36 deaths, E=25.7) was close to being beyond the bounds of chance variation.

A recent study by Black et al.²⁸ found that in the vicinity of the Dounreay facility there was a raised incidence of leukaemia in both birth and school cohorts, which was also in contrast to the results of Gardner et al.^{26,27}

The aforementioned studies of cancer occurrence in the vicinity of nuclear facilities in the U.K. and elsewhere were of an ecologic design, and as such share an important limitation. Studies of this type provide little insight into whether the excess leukaemia was caused by radiation exposures because exposure information was not available for individuals, and the effects of risk factors other than radiation could not be directly controlled. Whether the leukaemia was caused by radiation was further called into question because, based on the current understanding of the dose-response relationship between radiation and leukaemia, the observed excesses of leukaemia in the U.K. studies were much greater than could be accounted for by the known levels of radioactive emissions.²⁹ Therefore, the primary role of these ecologic studies has been to provide information about where to focus subsequent research efforts.

B.2 Risk Factors and Analytic Studies

Leukaemia is a heterogeneous disorder with a complex and poorly understood etiology, although several factors have previously been shown to be associated with an increased risk of childhood leukaemia. Established risk factors include: exposure to ionizing radiation after birth or prenatally; presence of a chromosomal abnormality such as Down's syndrome; and exposure to chemotherapeutic agents.³⁰ Evidence of etiologic importance is conflicting for factors such as other therapeutic agents, exposure to electromagnetic fields, chemical exposures of parents and viral infection. An increased risk of childhood leukaemia has been frequently reported for family

members and twins,³¹ but it is unclear if this is due to genetic or environmental factors. Childhood leukaemia rates are also known to have a four-fold international variation^{32,33} and to be higher in males, firstborn children and children of older mothers;³⁰ however, the etiologic importance of these observations is not known.

In order to examine the contribution of specific factors to the etiology of the Sellafield cluster of childhood leukaemia, a case-control study was performed. In this study, Gardner et al.^{1,2} examined whether the occurrence of leukaemia was associated with established risk factors, such as *in utero* exposure to x-rays, and with factors related to the nuclear facility (e.g., emissions, workers). The specific factor found to be associated with highest risk was that of fathers who worked in the nuclear industry and who had relatively high exposures to ionizing radiation around the time of their child's conception. For example, there was an eight-fold excess in leukaemia risk among children of workers who had either a lifetime external whole-body dose of ≥ 100 millisieverts (mSv) before conception (OR=8.4; 95% CI=1.4-52) or a dose of ≥ 10 mSv during the six-month period prior to conception (OR=8.2; 95% CI=1.6-42). Although Gardner et al.^{1,2} included cases of both leukaemia and lymphoma, the association with paternal radiation exposures was seen primarily with leukaemia.

As a possible explanation for the paternal radiation effect seen in their case-control study, Gardner et al.^{1,2} speculated that ionizing radiation might cause a mutation in a father's sperm that could be leukaemogenic in offspring. Gardner et al. also offered other possible explanations, including that the fathers who received a high external whole body radiation dose may also have received work-place exposure to other factors. Among such factors suggested were chemicals used in the reprocessing of nuclear fuel, and internal sources of ionizing radiation, such as plutonium or tritium.

Whether there is a causal relationship between paternal exposure to ionizing radiation and leukaemia in offspring is a hypothesis that requires verification. For the relationship to be causal, it must be plausible biologically. The biological plausibility of the hypothesis arises from (a) the fact that, at least at high levels, ionizing radiation can adversely affect genetic material, and (b) the observation that offspring could be affected in animals.^{34,35} The plausibility of the mechanism that underlies the hypothesis has also been argued using the analogy of retinoblastoma, which can arise from a germ-line mutation (i.e., in spermatogenesis) that affects the retinoblastoma gene.^{30,36} Nevertheless, there is also considerable evidence suggesting that the relationship is implausible.³⁷

An additional requirement for an association to be accepted as causal is that it must be consistently detected in epidemiologic studies. In fact, a major reason for scepticism about the above hypothesis is that such a result has not been consistently observed. In particular, leukaemia rates have not been elevated among the children of atomic bomb survivors.³⁸ Possible explanations for this discrepancy are that there may be different effects as a result of the different radiation dose rates received by atomic bomb survivors and the Sellafield workers^{1,2} and that there may have been differences in the length of time between exposure and conception.

Urquhart et al.³⁹ performed a case-control study in the Dounreay area and specifically examined whether there was an effect of exposure of fathers to radiation around the time of the child's conception, as seen by Gardner et al.^{1,2} The study by Urquhart and colleagues, which included only 14 cases of leukaemia and lymphoma (whereas Gardner et al.^{1,2} had 52 leukaemia cases),

did not confirm the paternal effect, but neither did it provide strong evidence against this effect, because results were extremely imprecise due to the small sample size.

McKinney et al.⁴⁰ performed a case-control study in three districts of northern England, including West Cumbria, where the Sellafield facility is located. Preconception exposure of fathers to radiation was among the parental occupational exposures that were found to be associated with childhood leukaemia. However, this result is difficult to interpret because it was largely dependent on cases who were previously included in the study by Gardner et al.^{1,2} The study by McKinney et al.⁴⁰ suggested that the effect of preconception radiation exposures was independent of the effects of chemical exposures, although the results must be interpreted cautiously because crude measures of exposure were employed. Due to the overlapping nature of the two studies, the results reported by McKinney et al. do not provide independent confirmation of the hypothesis that paternal radiation exposure may play a role in the etiology of leukaemia.

Therefore, the two recent case-control studies, which examined the effects of a wide range of risk factors, were not able to either convincingly confirm or refute the hypothesis that paternal radiation exposure is associated with childhood leukaemia; further research in a variety of settings is therefore necessary in order to test the hypothesis.

B.3 The Relevance of the Ontario Setting

In Ontario, it was feasible to test the hypothesis generated by Gardner et al.^{1,2} because (a) childhood leukaemia cases could be identified from the Ontario Cancer Registry (OCR), (b) parents of these children could be identified from birth certificates, and (c) data on occupational exposure to radiation were available from the National Dose Registry (NDR) and in some circumstances from employer records. The Canadian experience is also of interest because workers at Canadian nuclear reactors receive a substantial proportion (20-40%) of their total radiation exposure as an internal dose (largely due to tritium).⁴¹ In addition, the workers in Ontario do not receive the types of chemical exposures experienced by the workers involved in nuclear fuel reprocessing at Sellafield, and it is these chemicals which may have introduced some confounding in the study by Gardner et al.^{1,2}

C. OBJECTIVE

The primary objective of this study was to examine whether there is an association between the occurrence of childhood leukaemia and the cumulative occupational exposure of fathers to ionizing radiation prior to the time of conception. The study focused on the effect of radiation exposures received during employment in the nuclear industry in Ontario.

D. METHODS

D.1 Design

The study employed a case-control design, which was similar to that used by Gardner et al.¹ In a case-control study, a series of cancer "cases" is compared to a series of "controls" with respect

to their prior exposure history. For this study, the case series consisted of children who developed leukaemia and the control series included children who were similar to the cases in terms of date and place of birth, but who did not develop leukaemia. The exposure of primary interest was any occupational exposure of the fathers of these children to ionizing radiation.

D.2 Case Selection

Cases were children (ages 0-14 years) who died from (between 1950 and 1988) or were diagnosed with (between 1964 and 1988) leukaemia and were born to mothers who, at the time of the child's birth, resided in the vicinity of an operating nuclear facility in Ontario. Leukaemia was defined according to the Ninth Revision of the International Classification of Diseases (ICD-9; classes 204 to 208).⁴²

Cancer mortality data were available from the OCR beginning in 1950, therefore only cases occurring during or after 1950 were selected. Data regarding cancer incidence (i.e., newly diagnosed cases) were available from the OCR beginning in 1964. Leukaemia deaths were used as a proxy for leukaemia incidence for the period prior to 1964, at which time the survival rates for childhood leukaemia were very low. Cases occurring up to the end of 1988 were included since this was the most recent date for which complete information was available from the OCR.

The OCR achieves a high level of completeness of registration, which is, in part, due to the fact that cancer registration in Ontario is accomplished by the linkage of records from multiple sources. For leukaemia at all ages it has been estimated that registration is 95% complete.⁴³ For leukaemia in children the level of completeness may be even higher, as it has been previously recognized that childhood cancers were over-reported by the OCR. To overcome this problem, as a standard procedure, the OCR obtains additional information that permits the verification of diagnoses for childhood cancers.

In order to determine residence of parents at the time of a child's birth, birth certificates for children who were born in Ontario were reviewed at the Office of the Registrar General. From 1950 to 1963 a total of 778 childhood leukaemia deaths were identified from the OCR. In addition, there were 2577 incident leukaemia cases identified for the 1964-1988 period, for which birth certificates were found for 2507 (97%).

This study was specifically designed to examine whether exposure to radiation during work in the nuclear industry was associated with childhood leukaemia. In order to answer this research question as efficiently as possible, cases and controls were selected from the population which had at least a small chance of receiving the exposure of primary interest.^{44,45} Therefore, regions of Ontario were identified from which the labour-force for the nuclear facilities was likely to be derived. These regions are referred to as "worker areas". The six facilities that were considered were: the Pickering Nuclear Power Generating Station and the Bruce Nuclear Power Development, both of which are operated by Ontario Hydro; the Atomic Energy of Canada Limited facility at Chalk River; the Nuclear Power Demonstration station at Rolphton; the uranium refinery at Port Hope; and the uranium mines at Elliot Lake. Details of the period and type of operation of each of these facilities are listed in Table 1.

Table 1: Nuclear facilities in Ontario

Location	Nuclear Facility	Type of Operation	Years of Operation
1. Pickering	Pickering NGS*	Power generation	1971-present
2. Bruce	Bruce Nuclear Power Development	Power generation Heavy water production and waste management	1967-present
3. Chalk River	Atomic Energy of Canada Limited	Research and development	1944-present
4. Rolphton	Nuclear Power Demonstration NGS	Power generation	1962-1987
5. Port Hope	Eldorado Nuclear Limited (Cameco)	Uranium refinery	1935-present
6. Elliot Lake	Denison, Rio Algom and others	Uranium mine and mill	1954-present

* NGS = Nuclear Generating Station

The definition of the "worker areas" was based (where possible) on the residential distributions of the facilities' current labour forces. Labour force statistics were made available by Ontario Hydro for the Pickering and Bruce facilities [Green L: Personal communication] and by Atomic Energy Canada Limited (AECL) for its Chalk River location [Werner M: Personal communication]. The number of workers were obtained in areas defined by the first three digits of the postal codes and this was compared with the total male labour force as listed in census publications.⁴⁶ Contiguous postal code areas that had at least 0.5% of their labour force employed at the facility were included as part of the "worker area". This definition gave rise to areas that were quite large. For example, the "worker areas" for the Bruce and Chalk River facilities reached as far as 75 km from the facilities. Detailed labour force information was not available for the Port Hope or Elliot Lake facilities, therefore 25 km radius zones as employed by Clarke et al.³ were applied. Where boundaries overlapped, as for the Pickering and Port Hope facilities and the Chalk River and Rolphton facilities, a single "worker area" that represented both facilities was defined. The proportions of the regular work force of the nuclear facilities contained in each "worker area" was estimated to be 76%, 96% and 98% for the Pickering, Bruce and Chalk River facilities, respectively. Maps depicting the four "worker areas" are presented in Appendix A.

D.3 Case Confirmation

Initially, 113 cases were identified in the four regions. For these cases, the leukaemia diagnosis was verified by means of a review of pathology reports and other available information by a physician and, for cases that were considered doubtful by the physician, all information was reviewed by an oncologist with expertise in the diagnosis of leukaemia. Given that the case series included cases who were diagnosed many years ago, it was not possible to perform a

review of pathologic specimens. In the review of doubtful diagnoses, it was found that one "case" did not, in fact, have leukaemia, although the death certificate had listed a leukaemia of unspecified type (ICD-9 207.9). Accordingly, this individual was removed from the case series, thus leaving 112 cases.

Table 2 shows that 86.6% of the 112 cases were confirmed by pathology reports (i.e., histologically confirmed). For two of the 14 cases for whom pathology reports were not available, the diagnosis was confirmed to be leukaemia on the basis of other records (e.g., hospital progress notes or discharge summaries). For one case, the pathology report suggested, but did not confirm, a diagnosis of leukaemia; therefore, this case was included as a "possible" leukaemia. Of the remaining 12 cases, four incident cases could not be confirmed because additional information could not be obtained from the source hospitals and eight cases with a death certificate diagnosis of leukaemia could not be confirmed because no other records could be located (seven of these deaths occurred before and one occurred after 1964). The level of diagnosis confirmation was, therefore, lower for cases with death information only; however, it was important to include these leukaemia deaths in the case series because many occurred in the early period of nuclear facility operation (1950-1964).

Table 2: The level of confirmation of leukaemia diagnoses

Level of Confirmation	Number	Percent
Confirmed by pathology reports	97	86.6
Confirmed by other records	2	1.8
Possible leukaemia	1	0.9
Unconfirmed		
Incident case*	4	3.6
Death - died before 1964	7	6.3
- died after 1964	1	0.9
Total	112	100

* Records could not be found or were known to be destroyed.

D.4 Case Description

Table 3 shows, as was to be expected, that the number of cases in individual regions varied according to the total size of the population, with the majority residing in the region that contained the Pickering and Port Hope facilities. More of the cases were males than females (60% vs. 40%) and 70% of the cases were less than five years of age at the time of diagnosis or death. These observations are consistent with the widely recognized age and sex patterns of

leukaemia incidence.^{30,33,47} Cases arose with increasing frequency in the more recent years, with 50% of the case series arising from 1980 to 1988. This pattern of increasing frequency through the decades is due to growth in the populations of the regions covered by this study. The time trends of childhood leukaemia rates in Ontario are shown in Figure 1, which indicates that incidence rates have changed very little since 1964, whereas the mortality rates have declined since the 1950's.

Table 3: Region, sex, age and year of diagnosis or death for cases (n = 112)

	Number	Percent
Region		
- Pickering/Port Hope	69	61.6
- Bruce	21	18.8
- Chalk River/Rolphton	17	15.2
- Elliot Lake	5	4.5
Sex		
- female	45	40.2
- male	67	59.8
Age at diagnosis/death (years)		
- 0-4	79	70.5
- 5-9	22	19.6
- 10-14	11	9.8
Year of diagnosis/death		
- 1950-1959	6	5.4
- 1960-1969	15	13.4
- 1970-1979	35	31.3
- 1980-1988	56	50.0

The single most common type of leukaemia among the cases was acute lymphocytic leukaemia (62.5%; see Table 4). Table 4 also shows that, in total, 84% of the cases had a form of acute leukaemia, 3.6% had chronic leukaemia and 12.5% had other rare forms or an unspecified cell type. Chronic leukaemias occurred in 3.6% of the cases. Chronic lymphocytic leukaemia, which is generally considered to have no association with radiation, is extremely rare in children and did not occur among the cases for this study.

D.5 Control Selection

Birth certificates at the Office of the Registrar General of Ontario were used to identify controls. Controls were children who were matched to a case according to date of birth and mother's residence at the time of birth and who had not developed leukaemia or died by the time the index case was diagnosed. The matching by date of birth was achieved by searching through the birth certificates before and after the case entry to find a child born within three months of a case.

Figure 1: Leukaemia mortality and incidence among children (ages 0-14) in Ontario.

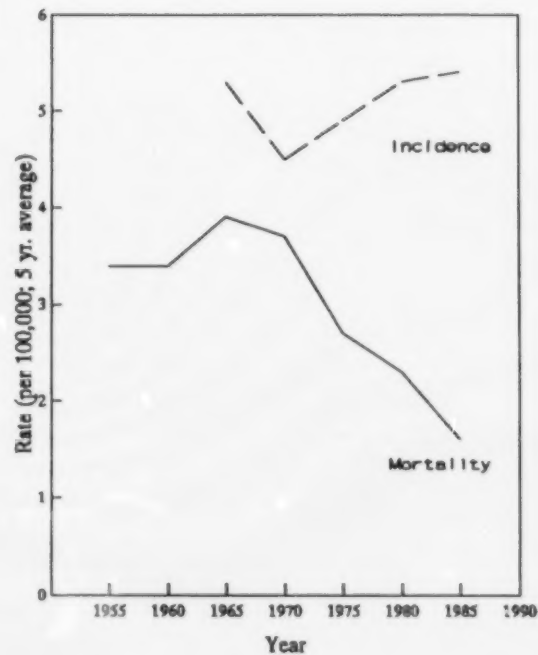


Table 4: The type of leukaemia for cases (n = 112)

Leukaemia Type	ICD-9 Code	Number	Percent
Acute lymphocytic	204.0	70	62.5
Acute myelocytic	205.0	14	12.5
Other acute leukaemia	206.0, 207.0, 208.0	10	9.0
Chronic leukaemia	205.1	4	3.6
Other	207.2, 207.8, 208.8, 208.9	14	12.5

Residence was matched by selecting controls whose mothers resided in the same "worker area" as the case. If twins were encountered in the birth certificate file (which occurred five times), only the first twin listed was included in the control series. Eight controls were selected per case in order to enhance the power of the study,⁴⁸ so that 896 potential controls were initially identified as the comparison group for the 112 eligible cases.

In order for the control children to have the same chance of developing leukaemia as the cases, they must have lived up to the age at which the case's disease was detected. Therefore, children who died prior to the development of the associated case's leukaemia were ineligible as controls. Premature death of the control children was identified by means of a computerized record linkage to Ontario death certificates. As a result of this mortality linkage, six controls were excluded, therefore, the control series used in the following analyses included 890 children.

The geographic regions from which cases and controls were selected were quite large. Therefore, even though the controls were matched to cases according to residence in a "worker area", it was recognized that the large size of these areas could allow controls to reside many kilometres from the case. Whether risk of leukaemia varied according to distance from a facility was examined in the analysis, thereby controlling for confounding that may have been present due to this variable.

D.6 Data Collection

Birth certificates were reviewed for both cases and controls to obtain father's name, place of birth, date of birth and/or age. Information was also obtained from the birth certificates regarding other variables that are possible risk factors of leukaemia (e.g., maternal age, birth weight and birth order).

Data pertaining to occupational exposure to radiation were obtained from the NDR, which is operated by the Bureau of Radiation and Medical Devices of the Department of National Health and Welfare. The NDR is a centralized system containing radiation dose records for all workers in Canada who are monitored for possible exposure to ionizing radiation and now contains data on approximately 410,000 individuals at 20,000 organizations since 1951.⁴⁹ For this study, a linkage was performed against the NDR in order to determine the cumulative radiation exposure of fathers of the case and control children. For each linked individual, the following data were obtained for each dose record contained in the NDR: the period of time that the dose referred to (period, annual, lifetime); the type of exposure (whole body external, tritium, radon progeny); the calculated dose (mSv, WLM); the employer; the job location; and the job class.

D.7 Record Linkage to the NDR

This section provides an overview of the procedures employed in the linkage to the NDR and how they were applied and evaluated. Details of the NDR linkage are presented in Appendix B.

The computerized record linkage procedure developed for this study was performed in two steps. First, all potential links in the NDR were identified on the basis of agreement of sex (male or missing), the "Soundex" encoded surname, initials of given names (in order, reversed, alternate or missing) and birth year (plus or minus two years). The file of all potential links was then

further processed to identify definite and possible links by assigning weights according to the relative frequency of the surname and the level of agreement in the surname, given names and date of birth. The assigned weights were derived from linkages that were performed at the Ontario Cancer Treatment and Research Foundation as part of the production of the OCR, using the Generalized Iterative Record Linkage System (GIRLS).⁵⁰ This linkage procedure was adopted because it was much more rapid and economical than either a manual linkage or a complete GIRLS linkage.

The completeness of identifying information on NDR records, which itself is dependent on the quality of data previously submitted, was found to be limited on many records (e.g., missing names, initials and birthdate); therefore, in order to resolve whether potential links were in fact links or non-links, it was necessary to obtain identifying information from employers (usually given names and date of birth). It was not feasible to try to obtain the extra identifying information for all of the thousands of individuals who were expected to arise as potential links; therefore, three additional linkage criteria were established.

As additional linkage criteria, it was required that the NDR file against which the linkage was performed would include only those who (a) were monitored for radiation exposure while working in Ontario, and (b) had a cumulative lifetime exposure greater than zero mSv. For the final linkage criterion, which related to the process of obtaining complete identifying information, a distinction was made between "nuclear workers" and "non-nuclear workers". A broad definition of "nuclear worker" was employed: those who worked in any stage of the nuclear fuel cycle in Ontario, that is, the mining, milling and refining of uranium, the manufacturing of fuel rods, or the development, construction, operation and maintenance of nuclear reactors. For all potential links who were nuclear workers, employers were contacted to obtain complete identifying information so that a more definitive linkage status could be assigned.

In contrast to nuclear workers, for individuals who had never worked in the nuclear industry, a greater degree of completeness in the NDR data was required for a link to be accepted. As a minimum, the information required in the NDR record for non-nuclear workers was surname, one initial and birth year. For example, with this rule a potential link for non-nuclear workers could be based on the agreement of "Mr. J Smith born in 1950", whereas for nuclear workers a potential link could be based simply on the agreement of "Mr. Smith". If a potential link was identified for a non-nuclear worker, then further information was sought from NDR records to try to verify the link. This distinction between nuclear and non-nuclear workers was made because it was feasible to obtain the extra identifying information necessary to resolve possible links only for nuclear workers since the majority of them were employed at a few large organizations.

In the preliminary stages of the NDR linkage, 86 definite and 129 potential links were identified (Table 5). After obtaining additional identifying information for the 129 potential links, an additional five definite (for a total of 91 definite links) and four probable links were identified. A link (either definite or probable) was, therefore, obtained for 9.5% (95/1002) of the individuals in the study.

Five general job classes were identified for the 95 individuals who linked to the NDR (Table 6). For these individuals, the most recent NDR report that contained a specific job class showed that

Table 5: The number of individuals linked to the NDR

Linkage Stage	Linkage Type	Number
Before Follow-up	Definite links	86
	Links requiring follow-up (potential links)	129
After Follow-up	Definite links	91
	Probable links	4

there were 52 reactor workers, 31 uranium miners, 10 workers in other industries, one medical worker and one for whom the job class was not available. Details of the job class definitions are listed in Table 6.

For the purpose of evaluating the linkage procedure, a number of individuals with known linkage status were added to the case-control series that was linked to the NDR. These individuals were included so that the linkage procedure could be evaluated in two ways: first, to see whether it obtained a link for 49 individuals who were known to be monitored for workplace radiation exposure; and second, to see if it obtained a non-link for 145 individuals who were known not to be listed in the NDR. The linkage procedure correctly classified all of the individuals in the evaluation dataset. Additional details of the evaluation of the linkage procedures are provided in Appendix B.

D.8 Radiation Dose Data

The computerized files of the NDR contain lifetime, annual and, in some circumstances, quarterly radiation dose histories for individuals exposed to several types of radiation (e.g., gamma, beta, x-ray, neutron, tritium, radon progeny). For every linked individual, a complete lifetime dose history, which included exposures arising in any province, was obtained from the NDR and, where possible, these doses were verified by comparison with employer records.

External and some internal radiation exposures were considered in this study, where the distinction between the two types of exposure arises from whether the radiation source is outside (external) or inside (internal) the body. External whole body dose, as obtained from the NDR, refers to dose arising from gamma radiation, high energy beta radiation and x-rays, and is expressed as dose equivalents (in mSv). In most NDR records, the exposure in milliroentgen (mR) has been converted to absorbed dose in air expressed in milligray (mGy) by a conversion factor of 0.01. The quality factor for converting absorbed dose in air to absorbed dose in tissue, expressed in mSv, was assumed to be 1.0 [Ashmore P: Personal communication]. For convenience in this report, the terms dose and dose equivalent are assumed to have the same meaning.

Table 6: Frequencies by job class for the 95 individuals who linked to the NDR

Summary Job Class	Job Description (NDR Code Number)	Frequency
Reactor Workers	Scientific/professional (500)	25
	Administration (510), Chemical and radiation control (530)	5
	Maintenance (540,550,560)	11
	Operations (580)	4
	Training (597) and Unknown	2
	Construction (598)	5
Uranium Miners	Underground miner (601)	31
Other - Industrial	Instrument technician (42)	2
	Other industrial worker (48)	8
	- Medical	1
Unknown	Not available (0)	1

The two types of internal dose information obtained from the NDR were (a) for reactor workers, tritium dose (mSv), which is a type of internal whole body exposure, and (b) for uranium miners, internal exposures to the lung due to radon and radon progeny. Tritium doses were determined from the concentration of tritium in urine. By means of a dose model, these concentrations were converted to a whole body internal dose expressed in mSv. The total whole body dose equivalent was obtained by adding together the external and tritium dose equivalents, which were also analyzed separately. Radon exposures were expressed in working level months (WLM), where one WLM is the exposure resulting from inhalation of air with a radon concentration of 1.0 working level (1.3×10^5 MeV of potential alpha energy arising from 1 litre of air) over a one month-period (170 working hours).⁵¹ In this report, the term radon is used to refer to both radon gas and radon progeny.

Lifetime and annual radiation doses were obtained from the NDR. Dose calculations were also made for the most critical periods that were identified by Gardner et al., namely the lifetime cumulative exposure ending at the time of conception (birthdate minus 270 days) and the total exposure during the six-month period prior to the child's conception. This approach was more precise than the method employed by Gardner et al.,^{1,2} which was to simply divide an annual dose in half to estimate a six-month dose.

If there is a true leukaemogenic effect of radiation that acts via male germ cells, then it is biologically plausible that the effect would be greatest for exposures during an interval that is even shorter than the six-month preconception period studied by Gardner et al.^{1,2} The duration

of the complete spermatogenic process in man, that is from the cell division that gives rise to a stem spermatogonium to the release of spermatozoa into the lumen of the seminiferous tubules, is estimated to be 74 days.⁵² Accordingly, the several generations of precursor spermatogonia and the spermatozoon that result in conception would have existed in the testis for approximately three months prior to conception. Therefore, in this study radiation dose was also estimated for the three-month period prior to a child's conception.

In order to permit the estimation of radiation dose for periods of specific interest, dose information, in as much detail as possible, was obtained from the NDR and from employers for the three-year period ending in the year of a child's birth. Where possible, individual dose measurements made on the basis of badge readings (or urinalysis for internal dose) were obtained. Detailed information of this type was obtained from computerized and microfilm records at the NDR and from large organizations that performed their own dosimetry (e.g., Ontario Hydro, AECL).

D.8.1 Variation in Procedures Used to Estimate Radiation Dose

There are many factors that may have affected the quality and consistency of the radiation dose data employed in this study. These factors include: for some individuals it was necessary to estimate preconception dose as it was not possible to refer to employer records or badge readings; reporting thresholds varied according to period of time and employer; the methods of calculating external dose varied between dosimetry services; Ontario Hydro tritium doses were pooled into a single lifetime value prior to 1975; the methods used to calculate tritium dose have changed over time; some dose histories were lost in a fire at AECL in 1956; and external doses for uranium miners had to be estimated on the basis of work histories for the period prior to 1981. Whole body external doses prior to 1981 were estimated for uranium miners as a function of job type, location, duration and period of time by the Uranium Facilities Division, at the Elliot Lake office of the Atomic Energy Control Board [Hore J: Personal communication].

Each of the factors that affected the calculated radiation doses is described in detail in Appendix C. Two strategies were followed in order to take these factors into account. First, dose data obtained from original source records were used to evaluate the quality of NDR data and to permit more detailed estimation of dose for preconception periods. Second, the sensitivity of the study results to these dose measurement problems was explored in the analysis.

D.9 Covariables

The primary exposure variable considered in this study was paternal radiation dose. Birth certificates provided information regarding other possible risk factors of childhood leukaemia, namely maternal age, birth weight, birth order and sex. The other available covariable was an indicator of the distance between a child's residence at birth (approximated by the centre of the census subdivision) and the nearest nuclear facility. For regression analysis, three categories of the distance variable were defined (0-14 km, 15-29 km, ≥ 30 km). The covariables were analysed individually to determine whether they were associated with the occurrence of childhood leukaemia, and in their role as potential confounders of the primary relationship under study.

D.10 Statistical Methods

The relative risk of developing leukaemia for each covariable level was estimated as an odds ratio (OR). In a case-control study, an odds ratio is a ratio of the odds of exposure among cases to the odds of exposure among controls. An odds ratio provides a valid estimate of relative risk when the disease is rare, as is leukaemia, and subject selection is unbiased. Odds ratios are presented with statistical tests of significance and 95% confidence intervals. Significance testing was performed using likelihood ratio tests and a two-tailed alpha probability of 0.05, and can be interpreted as a test of the null hypothesis that the risk of childhood leukaemia among those who were "exposed" is equal to the risk among individuals who were "not exposed" to a particular factor. For ordinal variables with more than two categories, a likelihood ratio test with one degree of freedom was performed to determine whether there was a linear trend in risk across the multiple categories (i.e., a simple trend test). When no cases contributed to the estimation of an odds ratio (i.e., 0 cases in a particular dose category), Fisher's exact test was used to test the null hypothesis on unmatched cases and controls and the result of this is presented as the probability of the observed distribution (p value). A 95% confidence interval for an odds ratio is a range of values that has a 95% chance of containing the true value. The width of a confidence interval provides an indication of the precision of the estimated odds ratio.

The statistical analysis was performed using conditional multivariable logistic regression analysis in EGRET.⁵³ Conditional analyses take into account the matched nature of the data in a study of this type, as the conditioning involves the comparison of matched sets of cases and controls (e.g., a case is compared to its matched controls). Odds ratios obtained using conditional analysis are distinct from those that could be estimated unconditionally as the cross-product ratio, although for the majority of the results the two estimates were very similar. The conditional analyses are presented so as to avoid the conservative bias that can occur if matched data are analysed as if they were unmatched.⁵⁴

Continuous variables were categorized based on the control distributions (e.g., quartiles) or categories of radiation dose that have been reported in previous studies (e.g., Gardner et al.^{1,2}). Additionally, maternal age greater than 35 was analyzed as a separate category.

Due to the fact that control children were matched to cases with regard to date and place of birth, it was not possible to analyze whether the occurrence of leukaemia was associated with age, period of time and region of the province. However, subanalyses were performed in order to examine whether there was variation in the odds ratios for radiation exposures across strata of the variables used in matching.

E. RESULTS

The linkage to the NDR resulted in the identification of 11 cases and 84 controls who were monitored for occupational exposure to radiation (Table 7). The odds ratio obtained by conditional regression analysis was 1.07, which can be interpreted as an indication that, relative to children whose fathers were never exposed to radiation in the workplace, the risk of leukaemia in children whose fathers were so exposed was 1.07 times (or 7%) greater. As shown by the 95% confidence interval (0.50-2.29) and the likelihood ratio test (0.03, 1 degree of freedom (df),

$p=0.86$), this result indicated that the risk of leukaemia was not significantly different between children whose fathers were and were not monitored by the NDR (i.e., this 7% elevation in risk is within the limits of chance variation).

Table 7: Frequency of cases and controls, odds ratios, confidence intervals and likelihood ratio tests by linkage status and general occupational class of father

Factor	Cases (n=112)	Controls (n=890)	Odds Ratios	95% CI	LR Test (df) and p value
Linked to National Dose Registry					
No (never exposed)	101	806	1.00	-	0.03 (1)
Yes	11	84	1.07	0.50-2.29	$p = 0.86$
Employed in Nuclear Industry					
Never exposed	101	806	1.00	-	
Non-nuclear worker	1	3	2.67	0.28-25.6	0.60 (2)
Nuclear worker	10	81	0.99	0.45-2.19	$p = 0.74$
Job Class					
Never exposed	101	806	1.00	-	
Reactor worker	4	48	0.64	0.22-1.86	3.96 (3)
Uranium miner	5	26	7.27	0.59-88.7	$p = 0.27$
Other (Industry, Medical, unknown)	2	10	1.59	0.34-7.44	

Abbreviations: CI = confidence interval;
LR = likelihood ratio;
df = degrees of freedom;
 p = probability.

Table 7 also shows that the majority of the fathers who linked to the NDR were employed in the nuclear industry, since 10 cases and 81 controls had been nuclear workers. In contrast to individuals who were never exposed to radiation in the workplace (i.e., "non-links"), nuclear workers had an equal risk ($OR=0.99$), whereas for the small number of non-nuclear workers (one case and three controls) the odds ratio was 2.67, with a very wide 95% confidence interval (0.28-25.6) that encompassed the value of 1.0.

A more detailed classification of paternal occupation indicated that for reactor workers, who constituted the majority of all nuclear workers, there was a lower than expected risk of leukaemia among children ($OR=0.64$), whereas workers in other industrial, medical or unknown fields had an odds ratio of 1.59. Again, confidence intervals were wide and include a value of 1.0. Uranium miners had an odds ratio of 7.27 with a 95% confidence interval of 0.59-88.7. The wide variation in odds ratios between job classes could have been due to chance, as shown by the very wide confidence intervals and the likelihood ratio test (3.96 on 3 df, $p=0.27$).

Table 8 presents estimates of relative risk associated with any radiation dose (i.e., greater than 0.0 mSv), prior to conception or diagnosis. Table 8 and subsequent tables list four general types of radiation exposures over four periods of time. The exposures considered were total whole body dose (in mSv), external whole body dose (mSv), tritium dose (mSv), and exposures to radon and its progeny (WLM). The periods of time considered were lifetime prior to the child's conception, the six-month period prior to the child's conception, the three-month period prior to the child's conception and lifetime prior to the child's diagnosis (or death).

Due to the fact that several individuals who linked to the NDR were first exposed after conception (or diagnosis), the number of exposed subjects is smaller in Table 8 than was shown in Table 7. For example, six cases and 53 controls had a total whole body dose of more than 0.0 mSv prior to conception, which resulted in an odds ratio of 0.87 and a 95% confidence interval of 0.32 to 2.34. Odds ratios very close to 1.0 were obtained for total whole body doses during both the six-month and three-month period prior to conception. Three cases and 11 controls received their first exposures between the time of conception and diagnosis, resulting in a total of nine cases and 64 controls with a total whole body dose greater than 0.0 mSv and an odds ratio of 1.19 (95% CI=0.51-2.73).

Results pertaining to the effect of external whole body doses greater than 0.0 mSv were virtually identical to those for total whole body dose. Tritium doses greater than 0.0 mSv prior to conception occurred in 14 controls but no cases, giving rise to odds ratios of 0.0 for each of the preconception intervals. The p values obtained from Fisher's exact test indicate that these deficits of leukaemia risk are not statistically significant. One case and seven controls had their first tritium exposure after conception but before diagnosis, resulting in an odds ratio that was slightly greater than zero but still very small (OR=0.36). Among miners, lifetime radon exposures greater than 0 WLM occurred amongst four cases and 22 controls, for an odds ratio of 2.80 with a very wide 95% confidence interval (0.39-20.0). For the shorter preconception periods (both six and three months) and for lifetime radon exposure before diagnosis, large but statistically unstable odds ratios of 5.17 (95% CI=0.53-50.1) and 7.89 (95% CI=0.68-91.0), respectively, were obtained.

Analyses of whether there was a dose-response gradient are presented in Table 9. With those who had a dose of 0.0 mSv as the baseline category, the odds ratio associated with a cumulative lifetime dose of 0.1-49 mSv was 0.80 (95% CI=0.26-2.47) and for a dose of 50 mSv or greater the odds ratio was 1.09 (95% CI=0.21-5.55). Analyses of the effect of cumulative lifetime doses at conception of 100 mSv or greater, which are not presented in Table 9, showed that five controls but no cases had exposures of this magnitude resulting in an odds ratio of 0.0. Due to the small numbers and the absence of such exposures amongst cases, the results are pooled for doses of 50 mSv or greater. The odds ratio and likelihood ratio test values indicate that there was no significant variation in the odds ratios across the three dose categories.

During the six-month period prior to conception the odds ratio for total whole body doses of 1-4 mSv was 0.80 (95% CI=0.17-3.66), while for doses of 5 mSv or greater the odds ratio was 1.13 (95% CI=0.30-4.21). In more detailed analyses of higher dose categories, it was seen that of the 21 controls and three cases with doses greater than 5 mSv, nine controls but no cases had exposures of 10 mSv or greater (OR=0.0). In the three-month period before conception, eight controls but no cases had doses of 5 mSv or greater (OR=0.0) and, of these controls, three had

Table 8: Frequency of cases and controls, odds ratios, confidence intervals and tests of significance by paternal radiation exposure (ever/never)

Paternal Exposure	Cases (n=112)	Controls (n=890)	Odds Ratio	95% CI	LR Test (1 df) and p value
Total Whole Body Dose (external plus tritium) - mSv					
Before conception					
0	106	837	1.00	-	0.08
≥0.1	6	53	0.87	0.32-2.34	p = 0.78
During 6 months prior to conception					
0	107	849	1.00	-	0.00
≥0.1	5	41	0.96	0.34-2.77	p = 0.95
During 3 months prior to conception					
0	107	849	1.00	-	0.00
≥0.1	5	41	0.96	0.34-2.77	p = 0.95
Before diagnosis					
0	103	826	1.00	-	0.15
≥0.1	9	64	1.19	0.51-2.73	p = 0.70
External Whole Body Dose - mSv					
Before conception					
0	106	837	1.00	-	0.08
≥0.1	6	53	0.87	0.32-2.34	p = 0.78
During 6 months prior to conception					
0	107	850	1.00	-	0.00
≥0.1	5	40	1.00	0.34-2.87	p = 0.99
During 3 months prior to conception					
0	107	850	1.00	-	0.00
≥0.1	5	40	1.00	0.34-2.87	p = 0.99
Before diagnosis					
0	103	826	1.00	-	0.15
≥0.1	9	64	1.19	0.51-2.73	p = 0.15
Tritium Dose (internal whole body dose) - mSv					
Before conception					
0	112	876	1.00	-	Exact test*
≥0.1	0	14	0.00	-	p = 0.25
During 6 months prior to conception					
0	112	880	1.00	-	Exact test*
≥0.1	0	10	0.00	-	p = 0.40
During 3 months prior to conception					
0	112	880	1.00	-	Exact test*
≥0.1	0	10	0.00	-	p = 0.40
Before diagnosis					
0	111	869	1.00	-	1.29
≥0.1	1	21	0.36	0.05-2.77	p = 0.26
Radon Exposure (internal lung dose) - WLM					
Before conception					
0	108	868	1.00	-	1.12
≥0.1	4	22	2.80	0.39-20.0	p = 0.29
During 6 months prior to conception					
0	108	873	1.00	-	2.54
≥0.1	4	17	5.17	0.53-50.1	p = 0.11
During 3 months prior to conception					
0	108	873	1.00	-	2.54
≥0.1	4	17	5.17	0.53-50.1	p = 0.11
Before diagnosis					
0	107	866	1.00	-	3.40
≥0.1	5	24	7.89	0.68-91.0	p = 0.07

Abbreviations: CI = confidence interval;
df = degrees of freedom;

LR = likelihood ratio;
p = probability.

*Fisher's exact test

Table 9: Total dose, frequency of cases and controls, odds ratios, confidence intervals and likelihood ratio tests by level of paternal radiation exposure

Paternal Exposure	Cases (n=112)	Controls (n=890)	Odds Ratio	95% CI	LR Test (df) and p value
Total Whole Body Dose (external plus tritium) - mSv					
Before conception					
0	106	837	1.00	-	0.19 (2)
0.1-49	4	39	0.80	0.26-2.47	p = 0.91
≥50	2	14	1.09	0.21-5.55	
During 6 months prior to conception					
0	107	849	1.00	-	0.14 (2)
0.1-4.9	2	20	0.80	0.17-3.66	p = 0.93
≥5	3	21	1.13	0.30-4.21	
Before diagnosis					
0	103	826	1.00	-	0.79 (3)
0.1-49	6	39	1.27	0.49-3.32	p = 0.85
50-99	1	14	0.62	0.07-5.00	
≥100	2	11	1.57	0.26-9.60	
External Whole Body Dose - mSv					
Before conception					
0	106	837	1.00	-	0.37 (2)
0.1-49	4	41	0.77	0.25-2.36	p = 0.83
≥50	2	12	1.29	0.23-7.00	
During 6 months prior to conception					
0	107	850	1.00	-	0.28 (2)
0.1-4.9	2	21	0.77	0.17-3.49	p = 0.87
≥5	3	19	1.27	0.33-4.82	
Before diagnosis					
0	103	826	1.00	-	1.51 (3)
0.1-49	6	41	1.21	0.47-3.13	p = 0.68
50-99	1	15	0.61	0.07-4.82	0.27 (1)*
≥100	2	8	3.00	0.33-27.3	p = 0.60
Radon Exposure (internal lung dose) - WLM					
Before conception					
0	108	868	1.00	-	1.86 (2)
0.1-49	2	16	1.89	0.21-17.3	p = 0.39
≥50	2	6	5.14	0.48-55.2	1.83 (1)*
					p = 0.18
During 6 months prior to conception					
0	108	873	1.00	-	2.54 (2)
0.1-4.9	3	13	5.30	0.48-58.5	p = 0.28
≥5	1	4	4.92	0.29-82.8	1.78 (1)*
					p = 0.18
Before diagnosis					
0	107	866	1.00	-	3.39 (2)
0.1-49	3	16	7.43	0.54-103	p = 0.18
≥50	2	8	8.54	0.54-135	2.52 (1)*
					p = 0.11

Abbreviations: CI = confidence interval;
df = degrees of freedom;

LR = likelihood ratio;
p = probability.

*Test of linear trend

doses of 10 mSv or greater. Due to the absence of cases with a dose of more than 5 mSv in the three-month preconception period, no further analyses of dose response could be performed and, accordingly, this period was not included in Table 9.

Slightly higher doses were observed in the analysis of lifetime total whole body dose to the time of diagnosis, with two cases and 11 controls having doses of 100 mSv or greater (Table 9). Across the categories of increasing dose (0.1-49, 50-99 and ≥ 100 mSv) the odds ratios were 1.27, 0.62 and 1.57. Confidence intervals and likelihood ratio tests indicated that there was no significant variation in risk across the categories of dose at the time of diagnosis.

The majority of total whole body dose arose from external exposures, therefore the results of analyses of external whole body dose were very similar to those observed for total dose (Table 9).

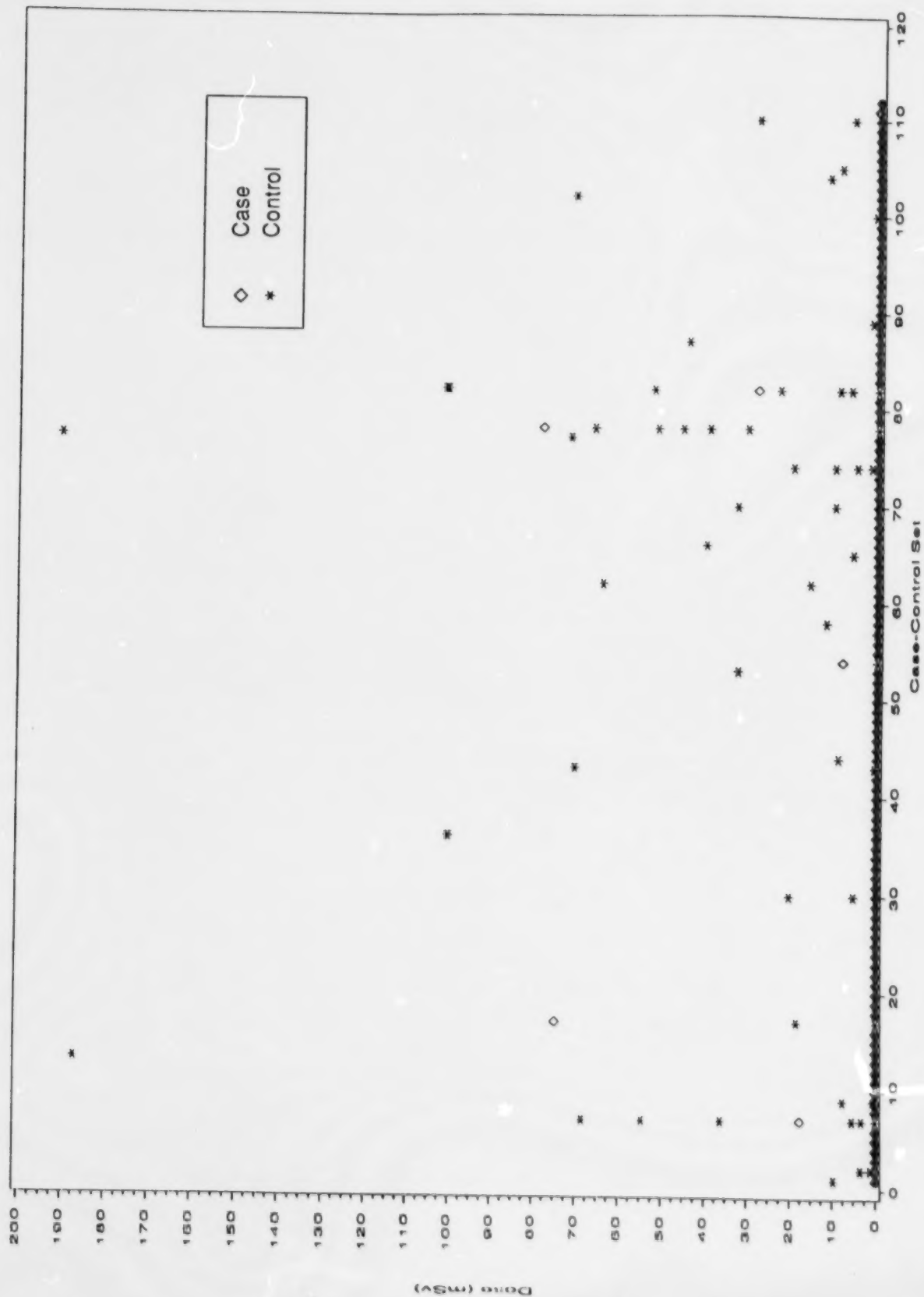
The primary differences between these two sets of analyses were that the number of subjects in the higher dose categories was reduced by no more than three individuals and that a higher odds ratio, which was not statistically significant, was achieved for doses of 100 mSv or greater at the time of diagnosis (OR=3.00, 95% CI=0.33-27.3). Results from the analysis of the three-month period before conception are not presented in Table 9 because exposure levels were very low, especially among cases, hence the odds ratios were similar to those shown previously in Table 8. Due to the fact that none of the cases had tritium doses, it was neither possible nor meaningful to further analyze the internal dose data with regard to dose-response.

Table 9 also shows that lifetime radon exposures of 0.1 to 49 WLM prior to conception had an odds ratio of 1.89 (95% CI=0.21-17.3), whereas for 50 WLM or greater the odds ratio was 5.14 (95% CI=0.48-55.2). Even though the odds ratios increased with increasing level of radon dose, the results were imprecise (i.e., wide confidence intervals) and no significant trend in the odds ratios was detected. Odds ratios for radon doses of 0.1 to 4.9 WLM and 5 WLM or more during the six months prior to conception were 5.30 (95% CI=0.48-58.5) and 4.92 (95% CI=0.29-82.8), respectively, with the latter being based on one exposed case and four exposed controls. Radon dose prior to diagnosis had odds ratios of 7.43 (95% CI=0.54-103) and 8.54 (95% CI=0.54-135) for doses of 0.1 to 49 WLM and 50 WLM or greater respectively. Again, all confidence intervals and statistical tests indicated that no significant associations or trends in relation to radon dose were detected.

The distribution of the total whole body dose in the 112 matched sets of cases and controls is plotted in Figure 2. This figure shows that the majority of subjects had doses of 0.0 mSv, that the majority of exposed individuals were controls and that the highest doses were received by fathers of control children. In only three case-control sets was the dose to the father of the case greater than the dose(s) to fathers of controls.

Further analyses of the dose data revealed that a large proportion of the individuals who received radiation exposures were uranium miners and that uranium miners constituted a relatively large proportion of the individuals who had higher radiation doses. For example, regarding total whole body dose prior to conception, both of the fathers of cases in the high dose category (≥ 50 mSv), two of the four fathers of cases in the low dose category (0.1-49 mSv), and seven of the 14 fathers of controls in the high dose category were uranium miners. Similarly, during the six-

Figure 2: Total dose prior to conception.



month preconception period, all three of the fathers of cases and nine of the 21 fathers of controls in the high dose category for total whole body dose (≥ 5 mSv) were uranium miners.

Table 10 presents analyses of the limited number of potential confounding factors that were available. Across categories of increasing maternal age (15-22, 23-26, 27-29, ≥ 30), there was a nonsignificant trend of decreasing odds ratios (from 1.0 down to 0.61). Further analyses of maternal age, which are not presented in Table 10, demonstrated that this pattern did not continue beyond a maternal age of 35 as the odds ratio in this category was 0.87 (95% CI=0.39-1.91).

Table 10: Frequency of cases and controls, odds ratios, confidence intervals and likelihood ratio tests by maternal age, birth characteristics, sex and distance from a nuclear facility

	Cases (n=112)	Controls (n=890)	Odds Ratio	95% CI	LR Test (df) and p value
Mother's Age					
15-22	35	219	1.00	-	4.02 (3)
23-26	36	262	0.85	0.50-1.41	p = 0.26
27-29	19	186	0.64	0.35-1.16	3.84 (1)*
≥ 30	22	223	0.61	0.34-1.08	p = 0.05
Child's Birth Weight (grams)					
< 3001	16	166	1.00	-	6.38 (3)
3001-3400	34	244	1.44	0.78-2.67	p = 0.10
3401-3685	35	205	1.76	0.95-3.29	
> 3685	19	217	0.92	0.46-1.83	
Child's Birth Order					
1	43	315	1.00	-	0.58 (3)
2	36	300	0.87	0.54-1.40	p = 0.90
3	17	144	0.83	0.46-1.51	0.44 (1)*
≥ 4	14	115	0.84	0.42-1.65	p = 0.51
Sex					
female	45	439	1.00	-	3.32 (1)
male	67	451	1.45	0.97-2.15	p = 0.07
Distance from Nuclear Facility (km)					
0-14	46	370	1.00	-	0.36 (2)
15-29	27	227	0.96	0.44-2.11	p = 0.83
≥ 30	39	293	1.17	0.55-2.49	

Abbreviations: CI = confidence interval;
df = degrees of freedom;

LR = likelihood ratio;
p = probability.

*Test of linear trend.

Odds ratios by birth weight quartile ranged from 0.92 to 1.76, which was not a statistically significant variation, and indicated that the lowest risks of leukaemia were in the lowest and highest birth weight categories. Birth order was not significantly associated with childhood leukaemia although the odds ratios indicated that leukaemia risk was slightly greater for firstborn children than for subsequent births. Males had a risk of leukaemia that was 1.45 fold greater than that of females, which achieved borderline statistical significance ($p=0.07$).

Overall, the average distance between the nearest nuclear facility and the children's residences at birth were equal for cases (mean=25.6 km, standard error=0.6) and controls (mean=24.3 km, standard error=1.7). Across the four worker areas, the mean distance was 8 km in the Elliot Lake area, 16 km in the Pickering/Port Hope area, 35 km in the Chalk River area and 45 km in the Bruce area. As shown in Table 10, the distance variable was not associated with childhood leukaemia, as there was no significant variation or trend in the odds ratios.

The impact of controlling for the potential confounding variables listed in Table 10 was explored by fitting multivariable logistic regression models. The results of the multivariable analyses are summarized in Table 11, which compares crude odds ratios (from Table 8) with adjusted odds ratios from the multivariable models. For total whole body doses, the adjusted odds ratios are slightly greater than the crude odds ratios for lifetime exposures before conception and diagnosis, whereas a small shift in the opposite direction to the odds ratio occurred for the six-month preconception dose. The adjustment for potential confounders had a greater effect on the odds ratios for radon doses in each of the three periods, with the direction being towards the null value ($OR=1.0$). The shift in the odds ratios was as large as a 17% reduction to the crude odds ratio of 5.17 for the six-month preconception period, which is an indication of the instability (due to imprecision) of the results regarding radon doses. Overall, there is no evidence of serious confounding by the variables that were available.

Table 12 presents frequencies and odds ratios for total lifetime whole body doses prior to conception stratified by region, age at diagnosis and period of diagnosis; variables that were closely associated with the matching factors. The stratification by region demonstrates that the largest number of subjects arose from the Pickering/Port Hope area, that the Bruce and Chalk River regions contributed similar numbers and that the Elliot Lake region contributed relatively few subjects. In contrast, the majority of the individuals with a preconception radiation dose greater than 0.0 mSv were from the Elliot Lake area (4 cases, 21 controls) whereas very few were from the Pickering/Port Hope area (one case, nine controls). In the Pickering/Port Hope area, one case father and two control fathers with a dose greater than 0.0 mSv were employed at the Port Hope facility. The odds ratios associated with a dose of 0.0 mSv or greater was 0.87 in the Pickering/Port Hope area, 1.00 in the Bruce area, 0.0 in the Chalk River area and 3.96 in the Elliot Lake area. As shown by the wide confidence intervals, no significant association was detected in individual regions.

Stratification by age at diagnosis demonstrated that the majority of the cases occurred prior to age five and that there was no significant variation in the odds ratios between the age strata (Table 12). Similarly, stratification by three periods of diagnosis indicated that there was no significant variation in the odds ratio for total whole body dose across time periods.

Table 11: Comparison of crude and adjusted odds ratios (adjusting for maternal age, birth weight, sex and distance in a multivariable model)

Factor	Adjusted*		Crude*	
	OR	95% CI	OR	95% CI
Total Whole Body Dose (external plus tritium) - mSv				
Before conception				
0	1.00	-	1.00	-
≥0.1	1.06	0.36-3.10	1.00	0.36-2.76
During 6 months prior to conception				
0	1.00	-	1.00	-
≥0.1	1.13	0.36-3.49	1.15	0.39-3.39
Before diagnosis				
0	1.00	-	1.00	-
≥0.1	1.47	0.60-3.61	1.34	0.57-3.13
Radon Exposure (internal lung dose) - WLM				
0	1.00	-	1.00	-
≥0.1	2.54	0.33-19.4	2.80	0.39-20.00
During 6 months prior to conception				
0	1.00	-	1.00	-
≥0.1	4.27	0.44-41.8	5.17	0.53-50.1
Before diagnosis				
0	1.00	-	1.00	-
≥0.1	7.24	0.56-92.5	7.89	0.68-91.0

*66 individuals with missing covariables were excluded from all analyses.
Abbreviations: OR = odds ratio;
CI = confidence interval.

It was possible to evaluate the quality of the dose data obtained from the NDR for 52 employees of AECL and Ontario Hydro. Two values of lifetime external dose and tritium dose prior to conception were estimated, one based on the NDR data and one based on the original source file of the employer. For 22 workers a dose of 0.0 mSv was reported from both data sources: six were monitored prior to conception but had no detectable exposure, whereas 16 had a dose of 0.0 mSv because they were not actually monitored until after conception. For 14 (27%) workers there was a discrepancy of more than 1.0 mSv; however, the difference was large enough to affect the allocated dose category (e.g., NDR dose of 46.8 mSv vs. Ontario Hydro dose of 52.9 mSv) for only one individual (a control). Figure 3 plots the difference (source minus NDR) between the two values of external dose by year for the 36 workers who were actually monitored prior to conception. Figure 3 shows that in general the discrepancies were very small and that they were greatest in the earlier periods of time (e.g., pre-1963). Tritium exposures were in general very low and were virtually identical in the two sets of records (e.g., there were only two discrepancies of more than 1.0 mSv and there were no changes in dose categorization).

Table 12: Frequency of cases and controls, odds ratios and confidence intervals by lifetime total whole body radiation dose to fathers prior to conception, stratified by region, age and period of diagnosis

Stratum	Dose (mSv)	Cases	Controls	Odds Ratio	95% CI*
Region					
Pickering	0	68	538	1.00	-
	≥0.1	1	9	0.87	0.11-7.06
Bruce	0	20	161	1.00	-
	≥0.1	1	8	1.00	0.11-9.07
Chalk River	0	17	119	1.00	Exact test p = 0.22
	≥0.1	0	15	0.00	
Elliot Lake	0	1	19	1.00	-
	≥0.1	4	21	3.96	0.38-41.8
Age at diagnosis (or death)					
0-4 years	0	75	595	1.00	-
	≥0.1	4	31	1.03	0.33-3.25
5-14 years	0	31	242	1.00	-
	≥0.1	2	22	0.57	0.09-3.67
Period of Diagnosis (or death)					
1950-1969	0	19	148	1.00	-
	≥0.1	2	18	0.85	0.15-4.80
1970-1979	0	33	264	1.00	-
	≥0.1	2	15	1.13	0.12-10.32
1980-1988	0	54	425	1.00	-
	≥0.1	2	20	0.79	0.18-3.52

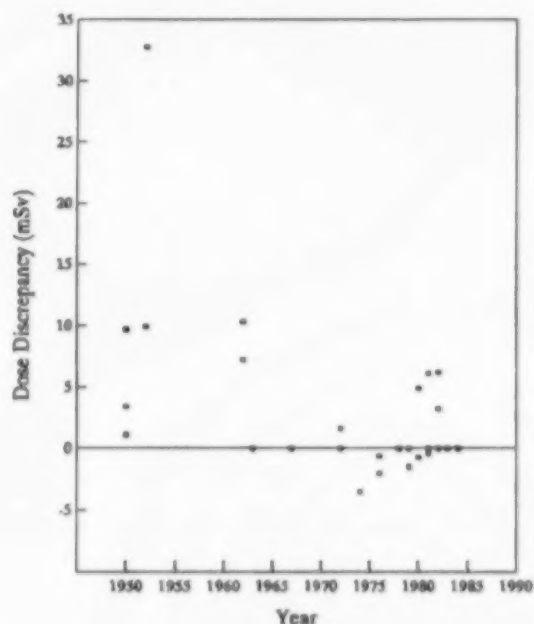
*CI= confidence interval; Fisher's exact test where specified.

F. DISCUSSION

F.1 Interpretation of the Results

The primary objective of this study was to assess whether paternal radiation exposures were leukaemogenic in offspring. The study considered the effects of both external and internal

Figure 3: External dose discrepancies
(OH or AECL value minus NDR value).



radiation during periods prior to conception or diagnosis while fathers were employed in a wide range of occupations. No statistically significant associations were detected between childhood leukaemia and paternal radiation exposures.

The primary focus of this study was the period of exposure prior to conception. There was, however, no evidence of an elevated risk in relation to exposures during the lifetime, six months or three months prior to conception, for each type of whole body exposure (total, external, internal). Doses during the three-month preconception period were low (e.g., no fathers of cases had a dose ≥ 5 mSv), therefore, meaningful analyses of dose response could not be performed. Exposures prior to the time of a case's diagnosis or death were also considered and found not to be associated with the disease. Odds ratios obtained for the pre-diagnosis period were slightly greater than for the preconception period, which is contrary to what would be expected if the preconception period was indeed the most important etiologically.

Relative risk estimates obtained for total and external whole body doses were very similar, largely because external exposures constituted the majority of the total dose. Gardner et al.² reported an association with external exposures, but also speculated that internal exposures may have contributed to the excess risk. The effects of internal exposures were considered in this

study, but they were found not to be associated with excess risk. On the contrary, none of the fathers of cases had tritium exposures. This suggests that in the Ontario setting, internal radiation exposures of fathers in the workplace were not associated with an elevated risk of childhood leukaemia.

In addition to the absence of an association with radiation exposures at any level, there was also no apparent gradient of effect with increasing radiation dose. For example, the odds ratios for total whole body doses before conception were 1.0, 0.80 and 1.09 for doses of 0, 0.1-49 and 50 or more mSv, respectively, which indicated that with increasing dose there was not a corresponding increase in risk.

Radiation levels that were specifically considered in this study included doses of 100 mSv or greater prior to conception and 10 mSv or more during the six months preceding conception, since these were reported by Gardner et al.² to be strongly associated with leukaemia risk around the Sellafield facility. The number of individuals in these high dose categories was small, however, the prevalence of such exposures was only slightly less than that reported by Gardner et al.² For example, in this study the prevalence of exposure among controls to lifetime preconception doses of 100 mSv or greater was 0.6% (5/890), whereas Gardner et al. reported a 1.1% prevalence (3/276 local controls). Regarding doses of 10 mSv or greater during the six-month preconception period, the prevalence among controls in this study was 1.0% (9/890), as compared with a value of 1.1% (3/276 local controls) in the Sellafield study. Among cases, however, the prevalence of such doses was 0% (0/112) in this study whereas it was 8.7% (4/46) in the Sellafield study. Therefore, the reason why this study did not confirm the previously reported strong association between high preconception doses and childhood leukaemia² was not because such exposures did not occur in Ontario, but rather because they did not occur among fathers of the cases.

The largest, but also the least stable, relative risk estimates seen in this study referred to uranium miners and their exposures to radon gas. The odds ratio for uranium miners was 7.27 (95% CI=0.59-88.7) and for radon exposures of 0.1 WLM or greater prior to diagnosis a similar odds ratio was obtained (OR=7.89, 95% CI=0.68-91.0). The analysis of total whole body dose stratified by region resulted in an odds ratio of 3.96 (95% CI=0.38-41.8) for the Elliot Lake region. The imprecision of these results, which was indicated by the wide confidence intervals, arose because a relatively small number of individuals contributed to a very small number of case-control sets. For example, in the Elliot Lake area only five cases of childhood leukaemia occurred between 1954 and 1988. Accordingly, there were five case-control sets and among these, the fathers of four of the five cases and 26 of the 40 controls were uranium miners.

This study was not designed to detect effects of exposures occurring in small subsets of nuclear workers, therefore the imprecision of the results for uranium miners was not unexpected. The similarity of the odds ratios for uranium miners and radon exposures is indicative of the fact that radon exposure levels were estimated on the basis of work history. Accordingly, the radon variables may actually be serving as proxy indicators of exposures to factors other than radiation which occur amongst uranium miners. It should be noted that if there was a true leukaemogenic effect among this subgroup, it is probably not attributable to radon itself because the very short half-lives of radon and its progeny result in virtually all of the exposure being to the lungs rather than other organs.³¹ Although it has been suggested that there may be an association between

leukaemia and the exposure of individuals to radon,⁵⁵ it has not previously been suggested that radon could affect offspring.

The impact of controlling for the few covariables that were available was that slight shifts in the relative risk estimates occurred. These multivariable analyses did not, however, alter the conclusions that could be drawn based on the univariable analyses.

Regarding the individual covariables, in general the patterns of childhood leukaemia risk were consistent with previous studies. The well established increased risk of leukaemia among boys³⁰ was seen in these data. The slight increase in leukaemia risk that was observed in association with increasing birth weight was consistent with reports by Fasal et al.⁵⁶ and MacMahon and Newill.⁵⁷ Several early studies reported significantly lower leukaemia rates at higher birth orders,^{11,57,58} which was consistent with the direction of the nonsignificant result that occurred in this study.

On the other hand, the observed pattern of decreasing risk with increasing maternal age was contrary to previous reports that have shown the opposite, especially for maternal ages greater than 40 years.^{11,56,57,58}

F.2 Validity Considerations

F.2.1 Potential Biases

Several factors can potentially threaten the validity of a case-control study. A primary concern for many case-control studies is recall bias, which arises if the exposure under study is recalled differentially by cases and controls. Recall bias did not compromise the validity of this study because the radiation exposure information was primarily obtained from a pre-existing registry.

Selection bias could occur in a study if cases (or controls) were included in (or excluded from) the study because of some characteristic they exhibited which was related to the risk factor under investigation.⁵⁴ In this study, such systematic differences between cases and controls probably did not occur because they were identified from a common data source (birth certificates) which was unrelated to the exposure of primary interest.

Matching of cases and controls by factors that are strongly related to exposure can potentially introduce confounding and reduce study power. By performing a conditional analysis which accounts for the matched nature of the data, as was done in this study, the possible confounding influence of the matched variables can be controlled. Matching by a variable which is a true confounder of the exposure-outcome relationship can enhance the power of a case-control study. However, if a matching variable is strongly associated with the exposure but not the outcome (i.e., it is not a true confounder), then the opportunity for differences in exposure prevalence may be diminished and the power of the study may be reduced (e.g., resulting in a decreased chance to detect a true association).⁵⁹ In this study, statistical power was enhanced by employing a large control series, which included eight controls for every case.

F.2.2 Uncertainty in Measuring Radiation Dose

Uncertainties in the measurement of exposure variables (e.g., radiation dose) can also threaten the validity of a case-control study. In this study, measurement errors probably occurred randomly among cases and controls since the measurements were routinely made by dosimetry services that were involved with workers, whereas the study outcome was cancer in offspring. Measurement error that occurs equally for cases and controls (i.e., nondifferential misclassification) has the effect of making estimated odds ratios closer to 1.0 than the true value.⁵⁴ In some unusual circumstances misclassification due to measurement error may affect cases and controls differently (e.g., if by chance measurement quality is linked to a confounder), therefore it is important to examine the potential biases that could arise.

The impact on the results was considered for several factors that gave rise to errors in the measurement of radiation dose in this study. A detailed discussion of each issue is presented in Appendix D. Factors that had a trivial effect on the measured doses and had no impact at all on the allocation of individuals to the various preconception dose categories included: that for two fathers it was necessary to estimate doses for the six and three-month preconception periods only on the basis of annual doses; the variation in reporting thresholds from 1951 to 1972; and that all tritium doses prior to 1975 were pooled for Ontario Hydro workers.

The measured radiation dose could potentially have been affected in a meaningful way due to several other factors, including: the reporting thresholds after 1973; the variability in the method of calculating external dose by different dosimetry services in Ontario; the historical changes to the methods of tritium dosimetry; the effect of records being lost in the AECL fire in 1956; and the estimation of external whole body doses for uranium miners.

Factors that could have influenced the measured dose levels affected the allocation of controls to dose categories more frequently than for cases, partly due to the fact that the largest radiation doses occurred among controls. Analyses of the impact of these types of measurement error indicated that, when applied to cases and controls for the relevant time period or occupation group, the revised odds ratios shifted closer to 1.0. The single exception to this observation was that for uranium miners, if it was assumed that their estimated external whole body exposures were underestimated by a factor of two, then the revised odds ratio would be slightly greater than the value found in this study for the high dose category. In general, these assessments indicate that errors in the measured levels of radiation dose did not result in bias that would cause this study to fail to detect a true association between paternal radiation exposure and leukaemia in offspring.

As a final point regarding the measured radiation dose, it should be noted that the dose data obtained from the NDR referred to occupational radiation exposures, whereas each individual would also be exposed to background radiation, a large part of which arises from ambient radon progeny in non-occupational settings. If there was variation in radon progeny or background radiation levels, it would not significantly compromise the validity of the study because cases and controls were matched by region.

F.2.3 Misclassification of Linkage Status

Another type of measurement difficulty that could potentially affect the validity of this study is that linkage status could be misclassified. Two types of misclassification are possible: true non-links could be incorrectly classified as links to the NDR or true links could be missed.

The certainty of the linkage status was high for 91 of the 95 linked individuals in this study. The four remaining fathers were classified as "probable links" and it is among these that the first type of misclassification could have occurred. All four of the "probable links" were fathers of control children, with three residing in the Pickering/Port Hope area and one residing in the Bruce area. Three of these individuals had an external radiation dose prior to conception of zero mSv and one had a very low dose (1.5 mSv). Due to the fact that "probable links" occurred only for controls who had negligible radiation doses, the resultant odds ratios in this study were not heavily influenced by the inclusion of these individuals.

The second type of misclassification could occur if true links were missed during the linkage to the NDR or if individuals who were truly exposed to radiation in the workplace were not included in the NDR. The failure to identify true links in the NDR could have resulted from the use of the linkage criterion which excluded all individuals who were listed in the NDR as having a cumulative lifetime dose of zero mSv, which could occur for anyone whose detected exposures were below the reporting threshold. The individuals who would be missed for this reason could have had only negligible or undetectable radiation exposures, and their misclassification as non-links would not affect the primary results of this study since the baseline categories for the estimation of relative risk included individuals who had either no exposure or a dose of zero mSv (i.e., only linkage status and job class results could be affected).

It is possible that true exposures could have been missed if individuals were missing from the NDR, which could have occurred if all records for a worker were completely destroyed in the fire at AECL in 1956. This could only have affected a small number of individuals since their monitoring for radiation exposures would have to have stopped prior to 1956. Furthermore, these individuals would have had relatively low radiation doses since some information was available at AECL for all individuals who experienced large exposures prior to the fire.

Finally, it should be reiterated that the linkage procedures were evaluated and it was found that they correctly classified all members of the evaluation dataset which consisted of individuals with known linkage status. Therefore, if any links were missed, they would have been few and they would primarily have been for individuals with very low or undetectable radiation exposures. Accordingly, there would have been little opportunity for this factor to have biased the results of this study which focus on radiation dose.

F.2.4 Detection of Non-nuclear Workers

In the record linkage that identified individuals who were monitored in the NDR, a distinction was made between nuclear and non-nuclear workers. Due to the requirement for non-nuclear workers to have more complete identifying information, it is possible that some true links with the NDR may have been missed. The availability of complete identifying information in the NDR is probably independent of the case-control status of the children in this study. If exposure

ascertainment was made incomplete under such circumstances then individuals could be misclassified, which could result in effects similar to those discussed previously regarding randomly occurring measurement error.

Among the 95 fathers who linked with the NDR, only four were non-nuclear workers. The predominance of nuclear workers among the linked individuals was probably due to the fact that, except for the Pickering-Port Hope area, the regions of the province covered by this study were largely rural. Accordingly, these areas contained a relatively small number of people employed in medical or other industrial fields where radiation was involved. The predominance of nuclear workers was, therefore, not likely to be an artefact of the linkage methodology which required complete identifiers for non-nuclear workers. Furthermore, it can be seen that a relatively small number of medical and industrial workers were excluded because a large proportion (98.0%) of medical and industrial workers of Ontario had complete identifying information in the NDR, and this proportion was greater than that for Ontario reactor workers (96.3%).

It appears, therefore, that the exposure information regarding non-nuclear workers was relatively complete. Nevertheless, the number of non-nuclear workers involved in this study is too small to permit separate analyses or interpretation of results for this subgroup.

F.2.5 Uncertain Leukaemia Diagnoses

The diagnosis of one case who was included in the case series of this study was classified as "possible leukaemia" during the review of diagnostic information. This case was born in 1967 in the worker area around the nuclear generating station in Bruce County. Neither the father of this case nor any of the fathers of the matched controls were linked to the NDR. Accordingly, if this case and the matched set of controls were excluded from the analysis, there would be a negligible impact on the estimated odds ratios because the only effect on the numbers used in the analysis would be a slight reduction in the denominators (the total number of cases and controls).

F.2.6 Emigration from Ontario

Emigration from Ontario could potentially affect the results of this study because leukaemia occurring amongst children who moved from Ontario would not be registered in the OCR. Thus, it is possible that some children used as controls in this study actually developed leukaemia. Such misclassification in the outcome status, if it did exist, would probably be independent of the primary exposure status (paternal radiation exposure), and as such, would cause the odds ratios to be closer to 1.0 than the true value.

The potential impact of emigration on the study results was assessed by calculating how many controls may have been misclassified. Based on the person-years of follow-up for controls, age-specific emigration rates and age-specific leukaemia incidence rates, the expected number of misclassified controls was 0.007. This indicates that it is unlikely that even one control was misclassified. Therefore, the study results are not affected by emigration from Ontario.

F.2.7 Summary of Validity Considerations

The potential effect on the validity of this study was considered for many factors and was found to be negligible except for some factors that affected the measurement of radiation dose and the classification of linkage status. It must be reiterated that any systematic variation in dose measurement or linkage classification at a specific point in time would affect the fathers of cases and controls equally. For example, if for a specific period the dose of a case father was underestimated, because of a procedure in use at that time, then the doses of fathers of the matched controls would also be underestimated in the same way. In such a situation, the biasing potential of the measurement error is small.

F.3 Statistical Power of the Study

The statistical power of a study is the probability that a true difference in risk of a specified size could be detected by a significance test.⁶⁰ The power of a study is a function of its sample size, the size of the relative risk, the prespecified alpha probability (0.05) and the proportion of the population that is exposed to the factor of primary concern. The ability of this study to detect important excesses of risk was determined by calculating its statistical power using a methodology designed for case-control studies with multiple controls per case.⁴⁸

The proportion of controls with a total whole body dose greater than zero prior to conception was lower in this study (6.0%=53/890) than in the case-control study by Gardner et al.² (14.5%=40/276 among local controls). Nevertheless, the sample size of this study (112 cases), which included more than two times the number of leukaemia cases than the Sellafield study (52 cases), was sufficient to provide more than 80% power to detect a true odds ratio of 2.5 or greater. For this exposure category, Gardner et al.² reported an odds ratio of 1.4, whereas an odds ratio of 0.87 was found in this study.

The proportion of controls exposed to a high radiation dose prior to conception (e.g., lifetime preconception dose ≥ 100 mSv) was more similar between the two studies, being 0.6% (5/890) in this study and 1.1% (3/276) in the Sellafield study. For a rare exposure such as a preconception dose ≥ 100 mSv, which was present in 0.6% of controls, this study had more than 80% power to detect excess risks of 7.6 or greater. Therefore, for high preconception radiation doses, this study had sufficient power to detect only very large relative risks.

A slightly different approach for interpreting study results, when there is a prior hypothesis of elevated risk, is to test the hypothesis that the observed odds ratio was equal to a pre-specified value. For example, for a total whole body dose of 10 mSv or greater during the six-month preconception period, the odds ratio in this study was zero (based on exposure of zero cases and nine controls), whereas Gardner et al.² reported an odds ratio of 8.2 in a comparison with local controls. The conditional probability of obtaining the observed data, under the assumption that the true odds ratio was 8.2, was 0.0019 (based on the hypergeometric distribution).⁵⁴ Therefore, for the high dose category (e.g., 10 mSv), it can be concluded with a high degree of certainty ($p=0.0019$) that the odds ratio estimated in this study was less than the value reported by Gardner et al. (8.2).²

F.4 Comparison with Previous Studies

These results are not consistent with the observation by Gardner et al.² of an association between childhood leukaemia and the preconception exposure of fathers to ionizing radiation. Gardner et al. speculated that the true cause of the significantly elevated leukaemia rates around Sellafield might be internal radiation exposures that could have occurred among the workers who had high preconception exposures to external radiation. Internal radiation exposures due to tritium were considered in this study and were found not to be associated with an excess risk of leukaemia in offspring. Therefore, in Ontario there was no support for the hypothesis regarding internal radiation exposures, although it should be noted that the primary type of internal exposure among Ontario workers (tritium) may be different from that of nuclear workers in the U.K.²

Gardner et al.² posed another possible explanation for the Sellafield findings: that workers who received high radiation exposures may have had concomitant exposures to toxic chemicals. Benzene and other organic solvents were used in the nuclear fuel reprocessing facilities in England and Scotland²⁹ and these chemicals have been reported to be possibly related to childhood cancer in previous studies.^{61,62,63} The case-control study by McKinney et al.,⁴⁰ which included individuals who were also in the study by Gardner et al.,^{1,2} suggested that paternal exposures both to radiation and chemicals were associated with leukaemia in children and that they acted independently. For the majority of nuclear workers in Ontario, exposures to toxic chemicals seldom occur; therefore, it was not possible in this study to test the hypothesis regarding the leukaemogenic effect of such chemicals. However, it was possible to examine the effect of preconception radiation exposures without the potentially confounding influence of chemical exposures.

In the case-control study in the vicinity of the Dounreay nuclear fuel reprocessing facility, preconception radiation exposures of fathers were not significantly associated with childhood leukaemia.³⁹ The odds ratio reported by Urquhart et al.³⁹ for an external radiation dose of 10 mSv or greater during the six-month preconception period was infinity ($p=0.21$), based on one of 12 cases and zero of 45 controls being so exposed, whereas for preconception doses of 100 mSv or greater the odds ratio was zero ($p=0.79$) as this exposure occurred in no cases and only one control. The results of the Dounreay case-control study were therefore imprecise because of the small numbers involved, but its failure to detect a significantly elevated risk in association with preconception radiation exposures was generally consistent with this study.

The ecologic study of leukaemia among children born in the vicinity of nuclear facilities in Ontario indicated that there was some variation, although it was not statistically significant, between the observed and expected frequencies of leukaemia. Clarke et al.³ reported that leukaemia rates were slightly lower than expected in the vicinity of the research and development facility at Chalk River, were approximately equal to the expected around the uranium mining, milling and refining facilities at Elliot Lake and Port Hope, and were slightly higher than expected around nuclear generating stations at Pickering and in Bruce County. In this case-control study, in each of the "worker areas" the odds ratio associated with paternal radiation exposures was less than 1.0, except for the Elliot Lake area where there was a large, but not statistically significant, excess risk of leukaemia risk among children whose fathers were uranium miners.

The results relating to uranium miners must be interpreted with caution for several reasons. Due to the fact that only a small number of study subjects (5 cases and 40 matched controls) arose from the worker area around Elliot Lake uranium mines, the results that pertained specifically to uranium miners are unstable. This study was designed specifically to explore the effect of preconception radiation dose and for uranium miners the odds ratio associated with this dose was less than that associated with mining itself. This observation is an indication that if there was a true excess of childhood leukaemia in the Elliot Lake area (which was not found by Clarke et al.³), then it was possibly due to an exposure occurring in uranium mines other than the whole body radiation doses that were directly examined in this study. Uranium miners are potentially exposed to a number of occupational hazards and since these were unmeasured in this study their impact could not be controlled in the statistical analysis. It should also be noted that no prior hypothesis or biological rationale exists that would suggest that uranium miners, in particular, had preconception exposures to some factor that was leukaemogenic in offspring. Therefore, the most reasonable explanation for the observations pertaining to uranium miners is that they were a chance finding.

F.5 Strengths and Limitations

The strengths of this study included that the case-control design permitted a direct assessment of the relationship between paternal radiation exposure and leukaemia among offspring. Due to the fact that population-based registries were used to obtain the primary exposure and outcome information, data quality was enhanced and certain potential biases (e.g., recall bias) were avoided. The existence of the NDR and the OCR made this study of the relationship between a rare exposure and a rare outcome feasible since it was possible to cover a forty-year period. In order to minimize misclassification of the exposure and outcome variables, cancer diagnoses and radiation doses were confirmed by referring to detailed source data where possible. Another strength of the study is that the quality of the linkage procedures and the radiation exposure data were evaluated and found to have attained a high level of accuracy and completeness.

One limitation of this study was that information was not available for all known risk factors of leukaemia. For example, one well established risk factor that could not be examined was prenatal exposure to radiation during diagnostic x-ray examinations of mothers during pregnancy. This study did not aim to consider all possible risk factors of the disease, but instead focused on the effect of paternal occupational radiation exposures. Given that the odds ratios relating to radiation doses were close to 1.0 and that there were no values that approached statistical significance, it is highly unlikely that true associations were missed as a result of confounding by risk factors, such as prenatal diagnostic irradiation, which could not be controlled in the analysis.

Another limitation was that the study had sufficient power to detect only large relative risks. Despite the fact that the study covered a long period of time and referred to a large population, this occurred as a result of the rarity of both the outcome (childhood leukaemia) and the primary exposure variable (high preconception radiation dose). In order to avoid this problem, a study would need to be done in a jurisdiction, probably outside Canada, that had either a larger population or had a greater prevalence of exposure to high preconception radiation doses.

F.6 Conclusions

On the basis of this study it is concluded that there was no association between childhood leukaemia and the occupational exposure of fathers to ionizing radiation prior to the time of conception. This conclusion applies in particular to radiation exposures arising from employment in the nuclear industry in Ontario, since this was the source of the majority of the fathers' exposures. Due to the use of detailed and verified dosimetry data it was possible to examine the effect of paternal exposures to both external and internal radiation in specific periods of time: no association was detected for either type of radiation or for any of the preconception or prediagnosis periods of radiation exposure. Odds ratios were close to 1.0 for all radiation dose categories and occupations except uranium mining, which had a larger odds ratio that was interpreted as a chance finding.

The impact of several factors that could potentially diminish the validity of this study was considered. There was no evidence of serious confounding by the covariables that were available, which included maternal and birth characteristics that were available from birth certificates. The sensitivity of the resultant odds ratios was also examined with regard to problems of measurement and classification, especially as these related to the calculated levels of radiation dose. In general, the potentially biasing factors that were considered had, at most, only a small effect on the resultant odds ratios and virtually no effect on the conclusions that were drawn from the results.

The findings of this study in Ontario are not consistent with the hypothesis that childhood leukaemia is associated with the occupational exposures of fathers to radiation prior to conception, as was found in the case-control study at Sellafield by Gardner et al.² Furthermore, it can be concluded with a high degree of certainty that the odds ratios estimated in this study were less than the value reported by Gardner et al.² for relatively high preconception dose categories.

The results of this study provide evidence against the existence of an association between childhood leukaemia and preconception paternal exposures to either whole body external radiation or tritium. Although the underlying cause of the excess leukaemia reported by Gardner et al.² remains unresolved, it is possible that other internal radiation exposures (e.g., plutonium) or chemical exposures may have been important contributing factors.

F.7 Recommendations

This study did not confirm the results of Gardner et al.;² however, in order to more fully assess whether there is consistency between studies of the effects of preconception radiation exposures to fathers, additional studies of this relationship are still warranted in other countries. Furthermore, given that the etiology of childhood leukaemia continues to remain largely unknown, additional research is required that goes beyond this study and considers the effects of the full range of potential risk factors. Such studies are currently under way in Canada and elsewhere.

REFERENCES

1. Gardner MJ, Hall AJ, Snee MP, et al.: Methods and basic data of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J* 1990; 300: 429-34.
2. Gardner MJ, Snee MP, Hall AJ, et al.: Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J* 1990; 300: 423-9.
3. Clarke EA, McLaughlin J, Anderson TW: *Childhood Leukaemia Around Canadian Nuclear Facilities - Phase II*. Ottawa: Atomic Energy Control Board, 1991.
4. Shimizu Y, Schull WJ, Kato H: Cancer risk among atomic bomb survivors: The RERF Life Span Study. *JAMA* 1990; 264: 601-4.
5. Boice JD, Blettner M, Kleinerman RA, et al.: Radiation dose and leukaemia risk in patients treated for cancer of the cervix. *JNCI* 1987; 79: 1295-1311.
6. Court Brown WM, Doll R: Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965; 2: 1327-32.
7. Court Brown WM, Doll R: Expectation of life and mortality from cancer among British radiologists. *Br Med J* 1958; 1: 181-7.
8. Matanoski GM, Sartwell P, Elliot E, et al.: Cancer risk in radiologists and radiation workers. In: Boice JD, Fraumeni F (eds), *Radiation Carcinogenesis: Epidemiology and Biological Significance*. New York: Raven, 1984, p. 83-96.
9. Ichimaru M, Ishimaru T, Belsky JL: Incidence of leukaemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki 1950-1971: Radiation dose, years after exposure, age at exposure and type of leukaemia. *J Radiat Res* 1978; 19: 262-82.
10. Stevens W, Thomas DC, Lyon JL, et al.: Leukaemia in Utah and radioactive fallout from the Nevada test site. *JAMA* 1990; 264: 585.
11. Stewart A, Webb J, Hewitt D: A survey of childhood malignancies. *Br Med J* 1958; 1: 1495-508.
12. Murray R, Heckel P, Hempelmann LH: Leukaemia in children exposed to ionizing radiation. *N Engl J Med* 1959; 261: 585-9.
13. Graham S, Levin ML, Lilienfeld AM, et al.: Preconception, intrauterine and postnatal irradiation as related to leukaemia. *Natl Ca Instit Monograph* 1971; 19: 347-71.

14. Viel JF, Richardson ST: Childhood leukaemia around the La Hague nuclear waste reprocessing plant. *Br Med J* 1990; 300: 580-1.
15. Hill C, Laplanche A: Overall mortality and cancer mortality around French nuclear sites. *Nature* 1990; 347: 755-7.
16. Poole C, Rothman KJ, Dreyer NA: Leukaemia near Pilgrim Nuclear Power Plant, Massachusetts. *Lancet* 1988; ii: 1308.
17. Jablon S, Hrubec Z, Boice JD, Stone BJ: *Cancer in Populations Living Near Nuclear Facilities*. Washington: National Institute of Health, 1990.
18. Hatch MC, Beyea J, Nieves JW, Susser M: Cancer near the Three Mile Island Nuclear Plant: Radiation emissions. *Am J Epidemiol* 1990; 132: 397-412.
19. Grosche B, Hinz G, Tsavachidis C: Leukaemia mortality and morbidity in Bavaria. In: *Health Effects of Low Dose Ionizing Radiation - Recent Advances and their Implications*. London: British Nuclear Energy Society, 1988.
20. Michaelis J, Keller B, Haaf G, Kaatsch P: Incidence of childhood malignancies in the vicinity of West German nuclear power plants. *Cancer Causes Control* 1992; 3: 255-63.
21. Craft AW, Openshaw S, Birch J: Apparent clusters of childhood lymphoid malignancy in Northern England. *Lancet* 1984; ii: 96-7.
22. Heasman MA, Kemp IW, Urquhart JD, Black R: Childhood leukaemia in Northern Scotland. *Lancet* 1986; i: 266.
23. Forman D, Cook-Mozaffari P, Darby S, et al.: Cancer near nuclear installations. *Nature* 1987; 329: 499-505.
24. Roman E, Beral V, Carpenter L, et al.: Childhood leukaemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in relation to nuclear establishments in the vicinity. *Br Med J* 1987; 294: 597-602.
25. Ewings PD, Bowie C, Phillips MJ, Johnson SA: Incidence of leukaemia in young people in the vicinity of Hinkley Point nuclear power station, 1959-1986. *Br Med J* 1989; 299: 289-93.
26. Gardner MJ, Hall AJ, Downes S, Terrell JD: Follow-up study of children born elsewhere but attending school in Seascale, West Cumbria (school cohort). *Br Med J* 1987; 295: 819-22.
27. Gardner MJ, Hall AJ, Downes S, Terrell JD: Follow-up study of children born to mothers resident in Seascale, West Cumbria (birth cohort). *Br Med J* 1987; 295: 822-7.

28. Black RJ, Urquhart JD, Kendrick SW et al.: Incidence of leukaemia and other cancers in birth and schools cohorts in the Dounreay area. *Br Med J* 1992; 304: 1401-5.
29. COMARE: Committee on Medical Aspects of Radiation in the Environment - Second Report: Investigation of the possible increased incidence of leukaemia in young people near the Dounreay Nuclear Establishment, Caithness, Scotland. London: Her Majesty's Stationery Office, 1988.
30. Doll R: The epidemiology of childhood leukaemia. *J R Statist Soc A* 1989; 152: 341-51.
31. Linet MS: Genetic factors. In: Linet MS (ed): *The Leukemias*. New York, Oxford Press, 1985, pp. 79-83.
32. Parkin DM, Stiller CA, Draper GJ, et al.: *International Incidence of Childhood Cancer*. Lyon; International Agency for Research on Cancer, 1988.
33. Linet MS, Devesa SS: Descriptive epidemiology of childhood leukaemia. *Br J Cancer* 1991; 63:424-9.
34. Nomura T: Parental exposure to X-rays and chemicals induces heritable tumours and anomalies in mice. *Nature* 1982; 296: 575-7.
35. Nomura T: Of mice and men. *Nature* 1990; 345: 671.
36. Wheldon TE: The assessment of risk of radiation-induced childhood leukaemia in the vicinity of nuclear installations. *J R Statist Soc A* 1989; 152: 327-39.
37. Evans HJ: Leukaemia and radiation. *Nature* 1990; 345: 16-17.
38. Yoshimoto Y: Cancer risk among children of atomic bomb survivors: A review of RERF epidemiologic studies. *JAMA* 1990; 264: 596-600.
39. Urquhart JD, Black RJ, Muirhead JM, et al.: Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. *Br Med J* 1991; 302: 687-92.
40. McKinney PA, Alexander FE, Cartwright RA, Parker L: Parental occupation of children with leukaemia in West Cumbria, North Humberside and Gateshead. *Br Med J* 1991; 302: 681-7.
41. Ontario Hydro, Radioactivity Management and Environmental Protection Department. Nuclear Generating Division Occupational Radiation Dose Summary, 1962 to 1978. Toronto: Ontario Hydro, 1980.
42. World Health Organization, Ninth Revision Conference, 1975. *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Vol. 1*. Geneva: World Health Organization, 1977.

43. Robles SC, Marrett LD, Clarke EA, Risch HA: An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988; 41: 495-501.
44. Poole C: Critical appraisal of the exposure-potential restriction rule. *Am J Epidemiol* 1987; 125: 179-183.
45. Schlesselman JJ, Stadel BV: Exposure opportunity in epidemiologic studies. *Am J Epidemiol* 1987; 125: 174-8.
46. Statistics Canada, Census of Canada, Ontario: Part 2, Profiles - Population and Dwelling Characteristics - Census Divisions and Subdivisions. Ottawa: Ministry of Supplies and Services, Canada, 1986.
47. Stiller CA: Descriptive epidemiology of childhood leukaemia and lymphoma in Great Britain. *Leukemia Res* 1985; 9: 671-4.
48. Breslow NE, Day NE: Statistical Methods in Cancer Research - Volume II - The Design and Analysis of Cohort Studies. Lyon: International Agency for Research on Cancer, 1987.
49. Ashmore JP, Sont WN, Davies BF: Analysis of medical workers dose records from the Canadian National Dose Registry. *Radiat Prot Dosim* 1991; 36: 79-83.
50. Howe GR, Lindsay J: A generalized iterative record linkage computer system for use in medical follow-up studies. *Comp Biomed Res* 1981; 14: 327-40.
51. BEIR IV - Committee on the Biological Effects of Ionizing Radiations, Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Washington, D.C.: National Academy of Science, 1988.
52. Courot M, Hochereau-de Reviers MT, Ortavant R: Spermatogenesis. In: Johnson AD, Gomes WR, Vandemark NL (eds). *The Testis*. New York: Academic Press, 1970, p. 390.
53. SERC (Statistics and Epidemiology Research Corporation), EGRET, Seattle: SERC, 1991.
54. Breslow NE, Day NE: Statistical Methods in Cancer Research - Volume I - The Analysis of Case-Control Studies. Lyon: International Agency for Research on Cancer, 1980.
55. Henshaw DL, Eatough JP, Richardson RB: Radon as a causative factor in induction of myeloid leukaemia and other cancers. *Lancet* 1990; 335: 1008-12.
56. Fasal E, Jackson EW, Klauber MR: Birth characteristics and leukemia in childhood. *J Natl Cancer Inst* 1971; 47: 501-9.
57. MacMahon B, Newill VA: Birth characteristics of children dying of malignant neoplasms. *J Natl Cancer Inst* 1962; 28: 231-44.

58. Stark CR, Mantel N: Effects of maternal age and birth order on the risk of mongolism and leukemia. *J Natl Cancer Inst* 1966; 37: 687-98.
59. Rothman KJ: *Modern Epidemiology*. Boston: Little, Brown and Company, 1986.
60. Last JM (ed). *A Dictionary of Epidemiology*. New York: Oxford University Press, 1988.
61. Fabia J, Thuy TD: Occupation of father at time of birth of children dying of malignant diseases. *Brit J Prev Soc Med* 1974; 28:98-100.
62. Lowengert RA, Peters JM, Cicioni C, et al.: Childhood leukaemia and occupational and home exposures. *J Natl Cancer Inst* 1987; 79: 39-46.
63. Buckley JD, Robison LL, Swotinsky R, et al.: Occupational exposures of parents of children with acute nonlymphocytic leukaemia: A report from the Children's Cancer Study Group. *Cancer Research* 1989; 49: 4030-37.
64. BEIR V - Committee on the Biological Effects of Ionizing Radiations, Health Effects of Exposure to Low Levels of Ionizing Radiation. Washington, D.C.: National Academy of Science, 1990.
65. Health and Welfare Canada, Report of the Working Group on Bioassay and In Vivo Monitoring Criteria to the Federal-Provincial Advisory Committee on Environmental and Occupational Health. Bioassay Guideline 2 - Guidelines for Tritium Dosimetry. Ottawa: Information Directorate, National Health and Welfare, 1983.
66. Johnson JR: The estimation of the effective dose equivalent from tritiated water exposures using tritium concentrations in urine. *Radiat Prot Dosim* 1982; 245-7.
67. Johnson JR: Internal dosimetry for radiation protection. In: Kase KR, Bjarngard BE, Attix FH (eds). *The Dosimetry of Ionizing Radiation*. San Diego: Academic Press, 1985, pp. 369-409.
68. ICRP (International Commission of Radiological Protection), Report on Committee II on Permissible Dose for Internal Radiation, Publication 2. New York: Pergamon, 1959.
69. Dunster HJ (ed), News and comments, *Health Physics* 1969; 17:389.
70. ICRP (International Commission of Radiological Protection), Limits for Intakes of Radionuclides by Workers, Publication 30. Oxford: Pergamon, 1979.
71. AECB (Atomic Energy Control Board) The Determination of Effective Doses from the Intake of Tritiated Water. AECB; Ottawa, 1987.
72. ICRP (International Commission on Radiological Protection), Recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press, 1977.

73. Howe GR, Weeks JL, Miller AB, et al.: A Study of the Health of Employees of Atomic Energy Canada Ltd.: IV - Analysis of Mortality during the Period 1950-1981. AECL; Chalk River, Report # 9442, 1987.
74. Muller J, Wheeler WC, Gentleman JF, et al.: Study of Mortality of Ontario Miners: 1955-1977. Toronto: Ontario Ministry of Labour, Ontario Workers' Compensation Board; Atomic Energy Control Board of Canada, May 1983.
75. Muller J, Kusiak R, Ritchie AC: Factors Modifying Lung Cancer Risk in Ontario Uranium Miners: 1955-1981. Toronto: Ontario Ministry of Labour, Workers' Compensation Board of Ontario, Atomic Energy Control Board of Canada, July 1989.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of: Dr. P. Ashmore, Dr. W. Sont and staff of the National Dose Registry, Bureau of Radiation and Medical Devices, Health and Welfare Canada; Mrs. V. Hunter, Ms. D. Nishri, Ms. P. Clarke, Ms. S. Wing, Ms. G. Morrison, Ms. D. Dale and her staff and Ms. M. Nemes of the Ontario Cancer Treatment and Research Foundation; Dr. D. Myers, formerly at Atomic Energy Canada Limited; Dr. D. Whillans, Mr. W. Christiani and Mr. R. Hirning at Ontario Hydro; Ms. M. Werner, Mr. B. Heinmiller and Mr. S. Linauskas at Atomic Energy Canada Limited; Mr. J. Hore at the Elliot Lake office of the Atomic Energy Control Board; Mr. R. Kusiak at the Ministry of Labour; Dr. A.R. Belch at the Alberta Cancer Board and Mrs. C. LaChapelle, Registrar General and her staff.

The advice and comments of the Review Panel, which included Dr. A. Arsenault, Dr. G.B. Hill, Dr. G.R. Howe, Dr. L. McIntyre and Dr. H. Marshall, have been invaluable, as were reviews received from Dr. R. Cartwright, Dr. G. Draper and Sir R. Doll.

GLOSSARY

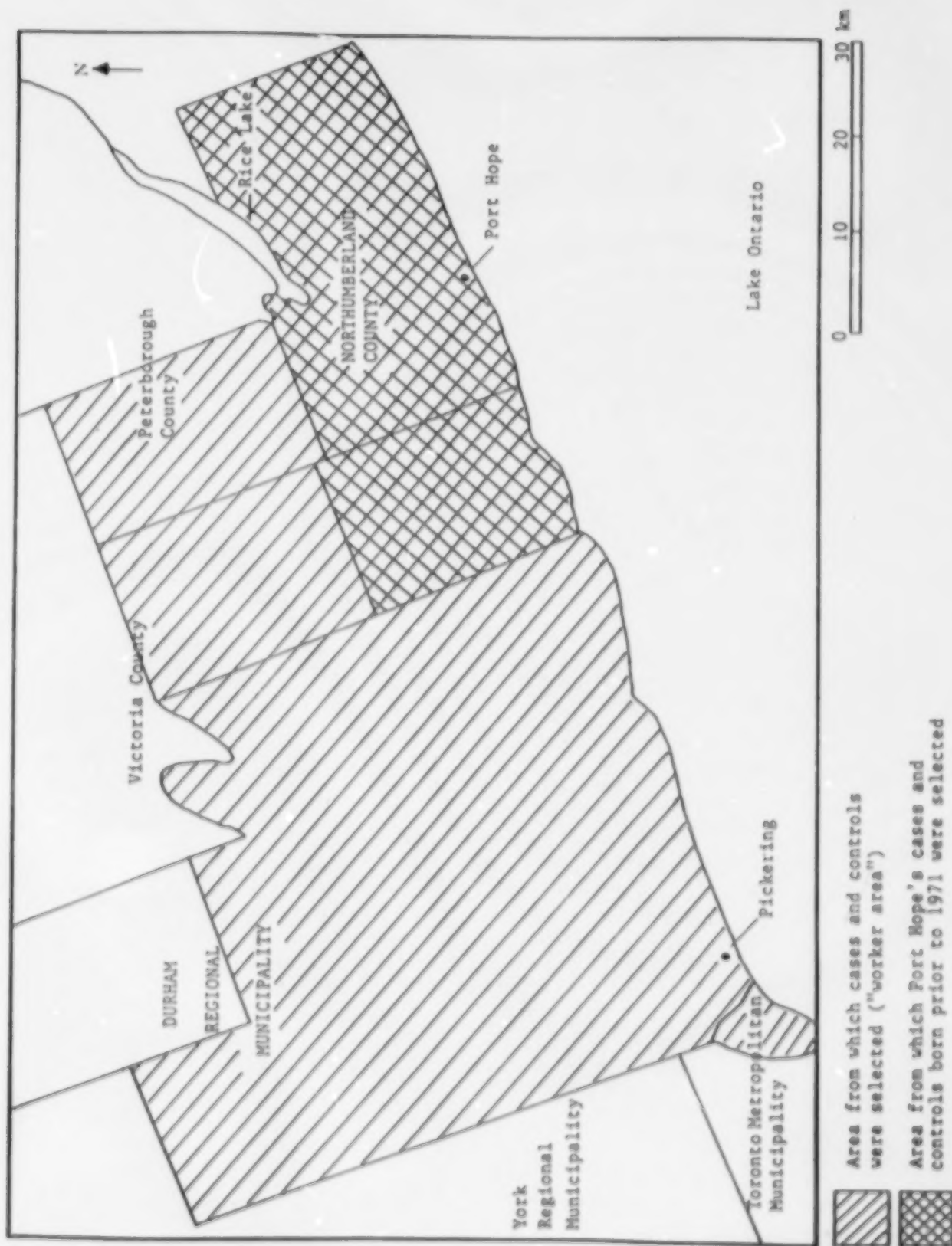
alpha probability	the probability of making the error of rejecting a true null hypothesis (synonym; Type I error).
association	a statistical dependence between two or more events, characteristics or other variables. ⁶⁰
attributable fraction	the proportion by which the incidence rate of disease could be reduced if the exposure was eliminated; it can be calculated to refer to the individuals who receive the exposure or to the general population. ⁶⁰
bias	deviation of results or inferences from the truth. ⁶⁰
case-control study	an epidemiologic study in which people with disease and a similarly composed group of people without disease are compared in terms of exposures to a putative, causative agent.
confidence interval	a 95% confidence interval is a range of values that has a 95% chance of containing the true value; it provides an indication of the precision of the estimated odds ratio.
confounding	a situation in which a measure of the effect of an exposure on disease risk is distorted because of the association between the exposure and other factors that influence the outcome under study. ⁶⁰
degrees of freedom (df)	the number of independent comparisons that can be made between the members of a sample; it refers to the number of independent contributions to a sampling distribution such as the χ^2 distribution to which the likelihood ratio statistic refers.
dosimetry service	an organization responsible for the estimation of radiation exposures on the basis of the analysis of personal dosimeter readings.
external whole body dose	whole body dose to tissues at a specified depth ("deep dose") arising from a radiation source that is outside the body; primarily due to gamma radiation and x-rays; expressed as dose equivalents (millisieverts).
incidence	the number of new cases of disease (e.g., cancer) in a defined population within a specified period of time. ⁶⁰

internal lung dose	the level of exposure of the lungs to ionizing radiation due to the inhalation of radon gas; expressed as working level months.
internal whole body dose	whole body soft tissue dose ("deep dose") arising from a radiation source that is inside the body; primarily due to tritium exposures of reactor workers; expressed as dose equivalents (millisieverts).
ionizing radiation	radiation sufficiently energetic to dislodge electrons from an atom; includes x-rays and gamma radiation, electrons (beta radiation), alpha particles (helium nuclei), and heavier charged atomic nuclei; neutrons ionize indirectly by colliding with atomic nuclei. ⁶⁴
leukaemia	a chronic or acute disease of unknown etiology characterized by unrestrained growth of leukocytes and their precursors. Leukaemia is a heterogeneous set of conditions, classified according to the dominant cell type and severity of the disease.
likelihood ratio test	a statistical test based on the ratio of the maximum value of the likelihood function under one statistical model to the maximum value under another statistical model; used in this study to test the null hypothesis of no association between childhood leukaemia occurrence and a variety of exposure categories.
linked individual	an individual who in the study was identified in the National Dose Registry following completion of the record linkage procedures.
National Dose Registry	a centralized system containing radiation dose records for all workers in Canada who are monitored for possible exposure to ionizing radiation in the work place.
non-nuclear worker	an individual who had never worked in the nuclear industry in Ontario (e.g., workers in medicine and other industries).
nuclear worker	an individual who worked in any stage of the nuclear fuel cycle in Ontario; that is, the mining, milling and refining of uranium, the manufacture of fuel rods, or the development, construction, operation and maintenance of nuclear reactors.
null hypothesis	the statistical hypothesis that one variable has no association with another variable; if the null hypothesis is true, then the results observed in a study would be no different from what might have occurred as a result of the operation of chance alone. ⁶⁵
odds ratio	a ratio of the odds of exposure among cases to the odds of exposure among controls; in a case-control study this provides an estimate of relative risk.

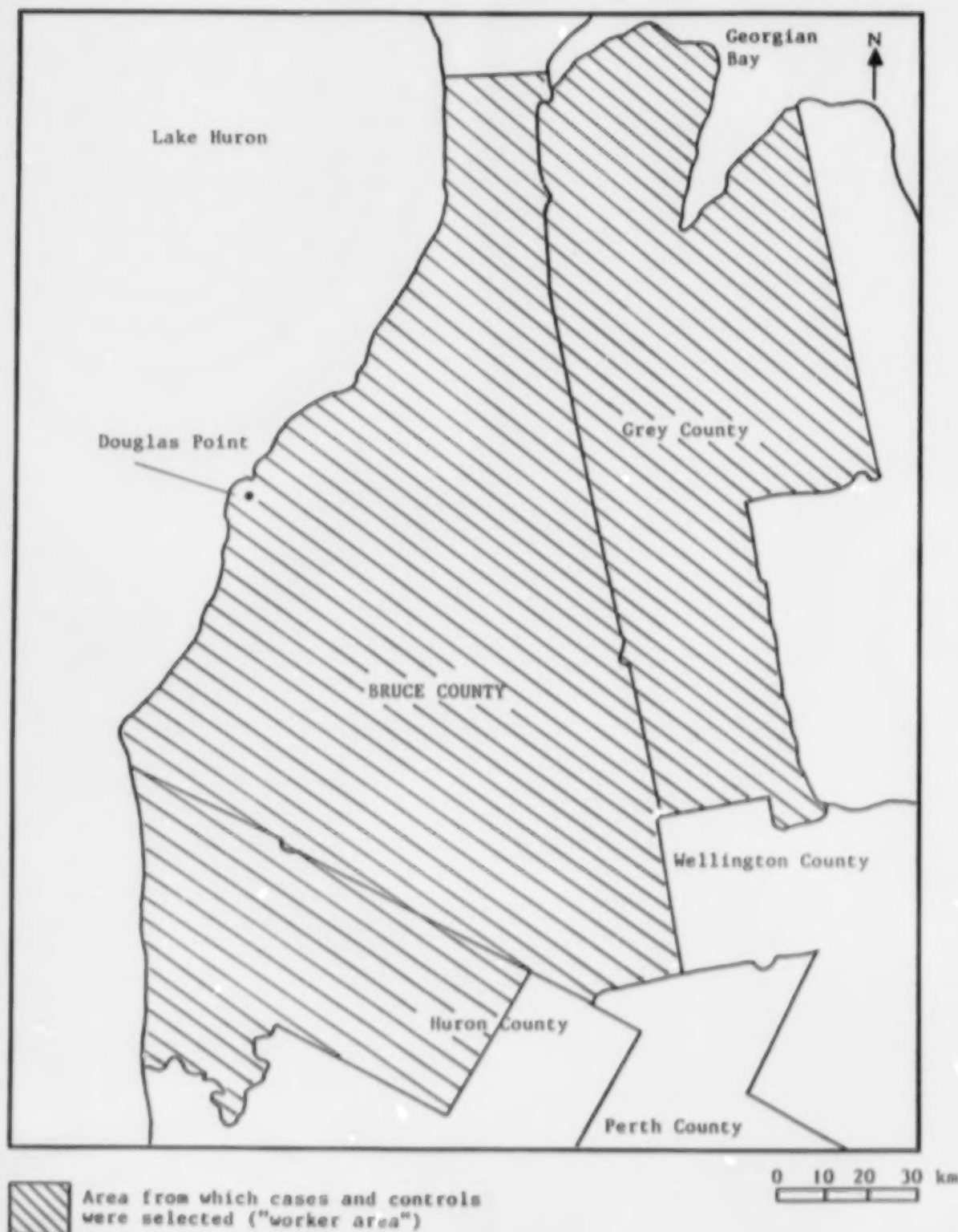
Ontario Cancer Registry	a database containing information about incident cancer cases in Ontario, beginning in 1964.
power	statistical power of a study is the probability that a true difference in risk of a specified size can be detected by a statistical significance test. ⁶⁰
prevalence	the number of instances of a given disease or attribute in a given population at a designated time. ⁶⁰
p value	the probability that a test statistic would be as extreme as or more extreme than observed if a null hypothesis were true; if the p value obtained in a statistical test is less than the pre-specified alpha probability, then the null hypothesis can be rejected and the results designated as "statistically significant".
radon	an inert gas formed by the radioactive decay of uranium-238 and radium-226. Radon gas has a short half-life (3.8 days) and decays to other radionuclides, known as radon progeny (e.g., isotopes of polonium, bismuth and lead). In this report, "radon" is used to refer to both radon and radon progeny.
reactor worker	an individual who worked in the development, construction, operation or maintenance of nuclear reactors; in this study, these were employees of Atomic Energy Canada Limited or Ontario Hydro.
relative risk	the ratio of risk of disease among the exposed to the risk among the unexposed; this can be estimated by an odds ratio. ⁶⁰
risk	the probability that an event will occur (usually referring to an unfavourable event). ⁶⁰
risk factor	an aspect of behaviour, life-style or environment or an inherited characteristic, which on the base of epidemiologic evidence is known to be associated with health-related conditions that are considered important to prevent. ⁶⁰
statistical significance	statistical methods allow an estimate to be made of the probability of the observed or greater degree of association between independent and dependent variables under the null hypothesis; in most biomedical and epidemiologic work, a study result whose p value is less than the pre-specified alpha probability (0.05) is considered sufficiently unlikely to have occurred by chance, thereby justifying the designation "statistically significant". ⁶⁰

total whole body dose	the sum of external whole body dose and internal whole body dose; expressed as dose equivalents (millisieverts).
tritium	a radioactive isotope of hydrogen which emits beta particles and has a half-life of 12½ years. ²⁹
worker areas	four regions of Ontario from which cases and controls were selected for this study; the area from which the majority of the labour force was obtained for nuclear facilities in Ontario.
working level months (WLM)	the exposure resulting from inhalation of air with a radon progeny concentration of 1.0 working level (1.3×10^5 MeV of potential alpha energy arising from one litre of air) over a one-month period (170 working hours). ³¹

"Worker Area" Around Pickering Nuclear Generating Station
and Port Hope Uranium Refinery



"Worker Area" Around Douglas Point Nuclear Generating Station
and Bruce Nuclear Power Development



"Worker Area" Around Chalk River Research and Development Facility and
 Rolphton Nuclear Power Demonstration Nuclear Generating Station

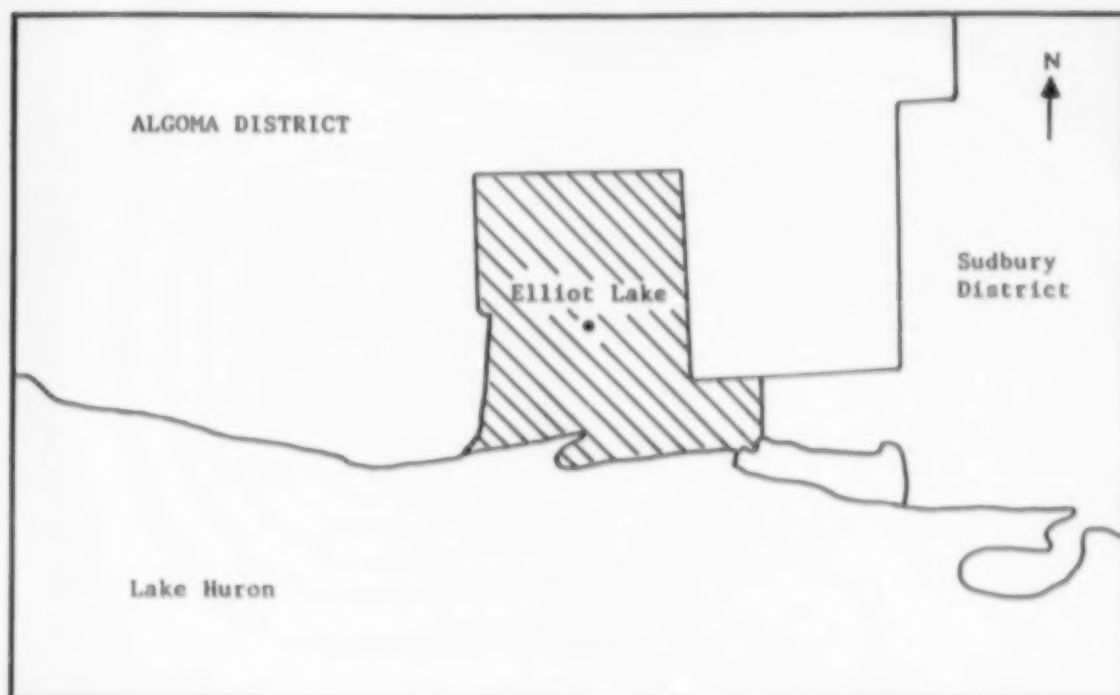


 Area from which cases and controls were selected ("worker area")

0 10 20 30 km


Nearby areas in Algonquin Park and Quebec, which were not included, were largely unpopulated.

"Worker Area" Around Elliot Lake Uranium Mine and Mill



 Area from which cases and controls were selected ("worker area")

0 10 20 30 km




Algoma District

PROCEDURES, APPLICATION AND EVALUATION OF THE RECORD LINKAGE TO THE NDR

B1 Procedures for Record Linkage to the NDR

In the first step of the record linkage, all potential links in the NDR were identified on the basis of agreement of sex (male or missing), the "Soundex" encoded surname, initials of given names (in order, reversed, alternate or missing) and birth year (plus or minus two years). In the second linkage step, the file of all potential links was further processed to identify definite and possible links on the basis of the level of agreement in the surname, given names and date of birth, where the assigned weights were derived from linkages performed at the Ontario Cancer Treatment and Research Foundation using the Generalized Iterative Record Linkage System (GIRLS).⁵⁰ This linkage procedure was adopted because it provided greater objectivity than a manual linkage and because it was much more rapid and economical than either a manual linkage or a complete GIRLS linkage.

The development of all linkage criteria and rules was completed prior to the main linkage and was based on the linkage of a test dataset of individuals who were neither cases nor controls in this study.

The ultimate goal of the linkage procedure was to distinguish links from non-links. For potential links it was intended that additional information would be obtained to supplement the NDR data, in order to clarify whether they were in fact a link or non-link. This additional information was to be obtained from employers by a letter (and follow-up telephone call) requesting the missing identifying information (usually given names and date of birth). However, during pilot testing of the linkage procedures, it became apparent that a very large number of potential links would arise (an average of 7.4 for every individual searched). The majority (81%) of these potential links occurred because the NDR contained a large number of records with incomplete identifying information (e.g., missing given names, initials and birthdate). In this study, it was neither feasible nor efficient to try to obtain the extra identifying information for all of the thousands of individuals who were expected to arise as potential links.

Additional criteria were therefore developed which minimized the number of potential links, but did not compromise the ability of the study to achieve its primary goal, which was to focus on radiation exposures arising in the nuclear industry in Ontario. These criteria were that the NDR file against which the linkage was performed would include only those who (1) were monitored for radiation exposure while working in Ontario, and (2) had a cumulative lifetime exposure greater than zero mSv. These criteria excluded a large number of potential links in the NDR that were largely irrelevant to the objectives of this study, however there were still more potential links than could be feasibly resolved. A further rule was therefore applied, whereby a distinction was made between "nuclear workers" and "non-nuclear workers" in terms of the strategies employed to obtain complete identifying information.

B1.1 Nuclear Workers

The primary focus of the study was on nuclear workers, whereas exposure to workers outside the nuclear industry was of secondary importance. A large number of the potential links were for

workers outside the nuclear industry (e.g., in other industries and health care) and it was for these workers that the task of obtaining complete identifying information would have been the most difficult (e.g., a large number of individuals or employers of only a few people would need to be contacted about workers from many years before).

A broad definition of "nuclear worker" was employed, so as to include the wide range of occupations that are connected with the facilities in the areas under study. The definition was based on variables in the NDR that indicated the job type or the employer. Nuclear workers were defined as those who worked in any stage of the nuclear fuel cycle in Ontario, that is the mining, milling and refining of uranium, the manufacturing of fuel rods, or the development, construction, operation and maintenance of nuclear reactors. Table B-1 lists the details of the job classes, the organizations and the locations that were included in the nuclear worker definition. In the calculation of cumulative radiation dose, all exposures were included regardless of whether or not they were from work in the nuclear industry.

Table B-1: Job classes, organizations and locations included in the nuclear worker definition.

General Job Class	Type of Work	Employer	Location
Power station workers	Scientific/professional, Administration, Chemical and radiation control, Maintenance, Operations, Security, Training, Construction, Custodial	Ontario Hydro	Pickering Bruce Romphon
Research and development	(as for power stations)	Atomic Energy Canada Limited	Chalk River
Nuclear fuel processors	Refining*	Cameco (formerly Eldorado)	Port Hope** (Ottawa, Blind River)
	Fuel fabrication	Zircatech (formerly Canadian Westinghouse)	Port Hope, Hamilton
	Fuel fabrication & pelletizing	Canadian General Electric	Toronto, Hamilton Peterborough
Uranium miners	Mining & milling	Denison, Rio Algom, Northspan, others	Elliot Lake & Bancroft

* The majority of nuclear fuel processors work in refining.

** Employees from Eldorado Head Office in Ottawa may have been exposed at the Port Hope location; a refinery at Blind River was also run by Eldorado, (beginning in 1983).

The nuclear worker definition included work places that were beyond the boundaries of the "worker areas" from which cases and controls were selected. It was recognized that these additional facilities were not major contributors to occupational exposures. Nevertheless, they were included in the nuclear worker definition because it was possible that people from the regions under study commuted to these facilities. Some industrial radiographers could receive radiation exposures at a nuclear facility, such as a nuclear generating station; however, they would be included as "nuclear workers" only if they were directly employed by the facility (as opposed to being contract workers).

The task of resolving the potential links was feasible for nuclear workers. This was because a smaller number of organizations needed to be contacted and because many of the individuals worked for two large organizations which had detailed and complete records on their past and current employees (e.g., Ontario Hydro and Atomic Energy Canada Limited).

B1.2 Non-nuclear Workers

For individuals who had never worked in the nuclear industry in Ontario a greater degree of completeness in the NDR data was required for a link to be accepted. As a minimum, the information required in the NDR record was surname, one initial and birth year. For example, with this rule a potential link could be identified based on the agreement of "Mr. J Smith born in 1950", whereas for nuclear workers a potential link could be based simply on the agreement of "Mr. Smith". If a potential link was identified for a non-nuclear worker, then further information was sought from NDR records to try to verify the link.

B2 Application of the NDR Linkage Procedures

The weighting process identified a bimodal distribution with a value of 400 distinguishing two groups of potential links. A potential link with a weight of 400 or greater was considered to be a "definite link". These definite links typically had complete information and full agreement on all identifiers.

All potential links with a weight of less than 400 were examined in greater detail. Included in these links was a small subset of individuals in the case-control file for whom identifying information was incomplete (e.g., missing birthdate). For these subjects a "non-link" was assigned if there was any disagreement on the available information (e.g., spelling of surname). NDR records with incomplete identifying information (e.g., only one initial or incomplete given name) remained as potential links and further information was sought.

In the first stage of the NDR linkage, approximately 1200 potential links for about 400 individuals were identified among the 1002 individuals (112 cases, 890 controls) who were searched. As shown previously in Table 5, 86 definite and 129 potential links remained after weighting and reviewing the linkages and, after obtaining additional identifying information for the 129 potential links, there were 91 definite and four probable links.

B3 Evaluation of the NDR Linkage

For the purpose of evaluating the linkage procedure, a number of individuals with known linkage status were added to the case-control series that was linked to the NDR. These individuals were

included so that the linkage procedure could be evaluated in two ways: first, to see whether it obtained a link for individuals who were known to be monitored for workplace radiation exposure; and second, to see if it obtained a non-link for individuals who were known not to be listed in the NDR. The evaluation dataset included 49 individuals who were known to be radiation workers ("atomic radiation workers" at Ontario Hydro) and 145 individuals who were known to have never been radiation workers (males who died before age 18; identified from death certificates). The staff who performed the linkage were not able to distinguish between subjects who were part of the main study or part of the linkage evaluation. The linkage staff were also blinded to the known exposure status of the individuals who were included as part of the linkage evaluation.

As shown in Table B-2, the initial linkage identified 48 of the 49 (98%) radiation workers as definite links and 132 of the 145 (91%) non-radiation workers as non-links. The remaining 14 records were included in the set of records for which further identifying information was sought by the NDR from the original suppliers of the data. Of these 14 records, one was confirmed as a definite link. This record was found to be for a radiation worker, giving rise to a "sensitivity" of the linkage procedure of 100% (49/49). Of the remaining 13 records that were further followed up, additional information was obtained for 10, all of whom were confirmed to be non-links. Therefore, 142 of the 145 non-radiation workers were confirmed as non-links. The remaining three non-radiation workers were classified as non-links because no further identifying information could be obtained and the available identifying information was not sufficient for linkage purposes. The linkage procedure therefore correctly classified all 145 of the non-radiation workers as non-links (i.e., a specificity of 100%).

Table B-2: A test of NDR linkage procedures to assess the accuracy of the classification of individuals as radiation or non-radiation workers (% of total in brackets)

True Status	Total	Number Correctly Classified	
		Before Follow-up	After Follow-up
Radiation Worker	49	48	49 (100%)
Non-radiation Worker	145	132	145 (100%)

It must be noted that the high level of accuracy achieved in linking the test datasets may be an overestimate of the actual accuracy of the main linkage for this study. This is due to the fact that the file of cases and controls may have greater variability in data quality than the test datasets, which were derived from only two sources (Ontario Hydro and death certificates).

DETAILS OF VARIATION IN PROCEDURES USED TO ESTIMATE RADIATION DOSE

C1 Dosimetry for External Radiation

There are a number of factors that may impact on the quality or consistency of the data in the NDR. The National Dosimetry Service was used in the monitoring of all Ontario workers except for employees of AECL, which has always performed its own dosimetry, and Ontario Hydro, which began its own dosimetry service in 1977. Different types of dosimeters have been used for monitoring gamma and x-ray exposures. "Film badge" dosimeters were initially used, but AECL changed to "thermoluminescent" dosimeters (using lithium fluoride) in 1973 and other users followed suit between 1977 and 1981. The frequency of reporting by the National Dosimetry Service changed from weekly reporting from 1951 to 1953, to biweekly reporting from 1954 to 1977. Longer wearing periods for low-risk National Dosimetry Service users were first introduced in 1969, with four-weekly monitoring, which continued until 1980. For a small number of individuals, eight-weekly monitoring was introduced in 1974 and continued to 1978. From 1980 to the present, only semi-monthly and three-monthly monitoring has been used by the National Dosimetry Service; (these frequencies were first introduced in 1977). At AECL, which submits reports to the NDR annually, dosimeters were changed weekly until 1958, after which they were changed biweekly. At Ontario Hydro, external dosimetry has always been run on a biweekly cycle, although reports are submitted to the NDR only on a quarterly basis.

Since 1951, there has been variation in the reporting threshold used by each of the dosimetry services. The National Dosimetry Service reporting threshold for gamma radiation and high-energy x-rays was set at 1.0 mSv in 1951, 0.2 mSv in 1954, 0.5 mSv in 1956, 0.4 mSv in 1958, 0.01 mSv in 1964 and 0.2 mSv in 1969. Values below the reporting threshold were recorded as zero, except during the period from 1964 to 1968, when they were recorded as 0.01 mSv. The AECL reporting threshold was 0.2 mSv until implementation of the thermoluminescent dosimeter program in 1973, from which time the threshold was 0.01 mSv [Ashmore P, Myers D, Heinmiller B: Personal communications]. As a result of these changes in reporting thresholds, it is possible that very low levels of exposure may not be reported in a consistent manner over the years.

The method of calculating external dose also varied between dosimetry services. In order to improve the consistency of reported dose levels arising from different organizations, the NDR made adjustments to data contributed by Ontario Hydro over specific time periods. For example, for the period 1977-1982, the NDR added 13% to the levels reported by Ontario Hydro because the NDR reported presumed whole body dose whereas Ontario Hydro reported only gonadal dose [Ashmore P, Christiani W: Personal communication]. This adjustment was discontinued in 1982, so that external doses reported by the NDR for Ontario Hydro workers since that time were actually gonadal. Beginning in the 1950's, AECL employed a dosimetric approach similar to that which was later employed by Ontario Hydro, but these gonadal doses were never adjusted by the 13% correction factor at the NDR because all historical AECL data were not added to the NDR until 1984 [Ashmore P, Myers D: Personal communication].

C2 Tritium Dosimetry

Tritium is a radioactive isotope of hydrogen which emits a beta particle upon decay. Because of its short track length (6 microns), tritium does not constitute a radiation hazard unless it enters the body.⁶⁵ Reactor workers employed by AECL and Ontario Hydro can be exposed to tritium in the form of either tritiated water (tritium oxide) or tritium gas. Tritium can enter the body by inhalation, ingestion and to a lesser degree by skin absorption.⁶⁵ Most of the body burden of tritium is excreted in urine, breath and perspiration with a half-life of 10 days, while a small fraction is incorporated into organic molecules.^{65,66,67}

Both AECL and Ontario Hydro perform their own tritium dosimetry and submit quarterly reports to the NDR. Annual tritium dose equivalents for AECL employees are reported in the NDR back to 1956; however, a systematic monitoring programme was not implemented until the late 1960s [Myers D: Personal communication]. Quarterly reporting to the NDR by Ontario Hydro began in 1975 and prior to that year only a single estimate of lifetime dose due to tritium is available in the NDR. (Hence, it was important to get detailed information from records at Ontario Hydro.) Tritium exposures are estimated on the basis of repeated urinalysis in which the excreted level of tritium is measured in becquerels/kilogram (previously $\mu\text{Ci/L}$). The average soft tissue dose equivalent due to tritium (in mSv) is then estimated as a function of the urine concentration of tritium, the time since the last urinalysis, and a dose rate conversion factor.^{65,66,67}

Over the past decades changes have been made to the recommended dose estimation procedures. In general, these changes have resulted in a reduction of the estimated dose associated with a particular level of tritium in the urine. These reductions have largely been due to revisions in the quality factor assigned to tritium's beta radiation, as recommended by the International Commission on Radiological Protection (ICRP). For example, in 1959 the ICRP recommended a value of 1.7 as the quality factor,⁶⁸ but this was revised to a lower level of 1.0 in 1969,⁶⁹ resulting in dose estimates that were 59% ($1.0/1.7$) of the earlier values. In 1979, a further reduction to about 67% of the previous level was recommended by the ICRP.⁷⁰ There was considerable delay before the international recommendations were implemented by Canadian facilities. For example, the recommendations of ICRP 1979, as modified by Health and Welfare Canada⁶⁵ and Johnson,⁶⁶ were formally applied in Canada in 1988,⁷¹ resulting in a tritium dose which was 73% of that calculated from 1970 to 1987 for a given level of tritium in urine.

The impact of the variation in tritium dosimetric practices is that calculated internal doses may not be consistent through time, with more recent dose levels being slightly lower than earlier reported levels for a given level detected in the urine.

C3 Records Lost Due to AECL Fire

In November of 1952 there was a reactor accident at the AECL facility, which was cleaned up between December 1952 and February 1954. Then, in 1956 many AECL records were destroyed during a fire in an administrative building. Records of individuals who had positive exposures (e.g., ≥ 20 mrem (0.2 mSv)) between weekly dosimeter readings prior to 1956 were not lost in the fire since multiple copies of their dose reports had been stored [Myers D: Personal communication]. For workers with lower levels of exposure, dose data were lost in the fire; therefore, efforts were made at AECL to reconstruct these lost dose histories. For each worker

the estimated value, as reported in the NDR, was a lifetime cumulative dose for the period ending in 1956. However, for most individuals, this was an underestimate of the true level because it consisted only of high exposures contained in the remaining reports. The maximum possible magnitude of this underestimation is 50 mSv/yr, which was the occupational dose limit used until recently,⁷² but it is likely that the underestimation was about 4 mSv/yr, which is the correction factor for annual doses at AECL prior to 1956 that has been employed in previous studies.⁷³

By referring to AECL records it was possible to estimate the dose for the pre-conception period in greater detail than would have been possible on the basis of NDR data alone. In addition to the reports of high exposures that occurred before the fire, AECL records contained information concerning the period of employment for each individual. There were 10 AECL workers for whom the relevant preconception period was prior to 1956. For five of these, their first employment (and radiation exposure) occurred after the child's conception. For the remaining five individuals, detailed employment and dosimetry information provided by AECL permitted the estimation of dose for the preconception period.

C4 Dose Estimation for Uranium Miners

For Canadian uranium miners, whole body exposure to radiation has been systematically monitored by personal dosimeter only since 1981, whereas the exposures dating back to 1950 were of interest in this study. Prior to 1981, information in the NDR concerning uranium miners was limited to their exposure to radon (which in this report includes radon progeny). Since 1977, quarterly radon reports have been routinely entered into the NDR for uranium miners.

Radon data in the NDR prior to 1977 were previously estimated on the basis of work history (e.g., job type, location, period of time and duration) as part of a large cohort study of Ontario miners.^{74,75} Beginning in 1955, information obtained during pre-employment and annual medical examinations of all miners in Ontario was entered into a computerized file known as the Mining Master File. For the purposes of the mining cohort study, the Mining Master File was modified by adding complete identifying information and work histories, resulting in the Work History File. The Work History was used to estimate the level of exposure to radon (in working level months), as the product of the concentration of radon for a particular mine and time (working level) and the duration of employment (months) at that time and in that location (corrected for deviations from normal working hours).⁷⁴ For the period from 1955 to 1967, radon concentrations were estimated for each mine, whereas beginning in 1968, area monitoring for radon gases began. The NDR contains estimates of annual radon exposures for uranium miners, dating back to 1955.

For the purposes of this study, a similar process was employed for the estimation of external whole body exposure to radiation whereby duration of exposure, based on work history, was multiplied by a dose rate conversion factor. For each miner identified during the NDR linkage, a request was submitted to the Ministry of Labour for information from the Work History File regarding the mine(s), occupation(s), years of employment and the total duration of employment per year. The duration of employment (hours) was then multiplied by a dose rate conversion factor (milliroentgen (mR) per hour) that was a function of ore grade (varied by mine and year). The level of exposure (mR) was interpreted as absorbed dose (mrad), under the assumption that the exposure-to-dose conversion factor for high energy radiation was close to 1.0. The absorbed

dose (mrad) was then interpreted as a dose equivalent in mrem, under the assumption that the quality factor was 1.0. The dose in mrad was then converted to mSv by dividing by 100.

The work history information was submitted to the Uranium Facilities Division, at the Elliot Lake office of the Atomic Energy Control Board (AECB), where external whole body exposures prior to 1981 were estimated [Hore J: Personal communication]. Since dose estimation of this type is routinely conducted by the AECB for the purposes of radiological protection, the AECB staff had access to employment records and were therefore able to confirm, and in some situations correct, the relatively crude estimates of employment duration that were available from the files of the Ministry of Labour. The AECB staff who performed the dose estimation were unaware of whether the miners were fathers of cases or controls.

This study considered mining exposures arising primarily in the Elliot Lake area even though uranium has also been mined in the Bancroft area. The Bancroft facilities were not formally included in this study because only a small number of mines (four) have operated in this area for a limited period of time (1954-1965, 1975-1977), whereas a large number of mines (16) have operated over a long period of time in the Elliot Lake area (1955-present).⁷⁴ In their historical review of uranium mining, Muller et al.⁷⁴ reported that 83% of the Ontario uranium miner cohort worked in the Elliot Lake area. For miners who worked at both Bancroft and Elliot Lake, estimated radiation exposures would include those arising from both locations.

THE IMPACT OF UNCERTAINTY IN RADIATION DOSE MEASUREMENT

The impact on the results was considered for the factors described in Appendix C, which could give rise to errors in the measurement of radiation dose in this study. Several of these factors had a trivial effect on the measured doses and had no impact at all on the allocation of individuals to the various preconception dose categories. The factors that produced negligible measurement errors included the following:

- (1) For two fathers who were identified in the NDR, detailed dose reports were not available, therefore, it was necessary to estimate doses for the six- and three-month preconception periods only on the basis of annual doses. No error was introduced, however, because for both individuals the annual dose in the period around the time of conception was 0.0 mSv.
- (2) Variation in reporting thresholds could have caused cumulative external doses to be either over or under-estimated. From 1964 to 1968 slight over-estimates (less than 1.3 mSv over five years ($0.01 \text{ mSv} \times 26 \text{ readings/year} \times 5 \text{ years}$)) could have resulted since a constant value (0.01 mSv) was added to all reports below the threshold. From 1951 to 1963 there could have been slight under-estimates (no more than 2.99 mSv ($0.009 \times 26 \times 13$)), since 0.0 mSv were reported for values below the reporting threshold, which was 0.01 mSv.
- (3) The fact that all internal doses prior to 1975 were pooled for Ontario Hydro workers could have made it difficult to estimate internal doses for the six- or three-month preconception periods. Such a problem did not occur in this study because all five of the Ontario Hydro workers who had children prior to 1975 had preconception doses of 0.0 mSv (four of the five received their first exposures after conception and one had a total dose of zero prior to diagnosis). No measurement error occurred as a result of this dose practice.

The measurement of radiation dose was potentially affected in a meaningful way due to several other factors. The impact of such measurement error on the estimated odds ratios was examined, in particular to determine the likely direction and magnitude of any potential bias.

- (1) From 1969 to the present, zero mSv were reported for values below the reporting threshold of 0.20 mSv. In the highly unlikely event that an individual repeatedly had a value just below the reporting threshold, the underestimation could have been by as much as 4.9 mSv per year ($0.19 \text{ mSv} \times 26 \text{ reports/year}$). All dose data were reviewed to determine what the impact on dose categorizations would be if 4.9 mSv were added to values that were reported as zero for the period after 1973. This adjustment to lifetime preconception external doses resulted in a maximum increase of 19.6 mSv. Two cases and five controls changed from the baseline category (0.0 mSv) to the low dose category (0.1-49 mSv), while three controls changed from the low dose to the high dose category ($\geq 50 \text{ mSv}$). The unconditional odds ratio for the low dose category after this adjustment to the calculated dose was 0.9, as compared with an unconditional odds ratio of 0.8 prior to making the adjustment. For the high dose category ($\geq 50 \text{ mSv}$) the

unconditional odds ratio after this adjustment was 1.1, as compared with a pre-adjustment odds ratio of 1.3. Therefore, in the unlikely event that individuals repeatedly had exposures that were slightly less than the reporting threshold, the impact of reporting their dose as 0.0 mSv could have introduced a conservative bias into the study results whereby the odds ratio reported in Table 9 would be further from 1.0 than the true value.

- (2) The impact of the variability in the method of calculating external dose by different dosimetry processors in Ontario was assessed by recalculating lifetime preconception dose. This entailed adjusting the values reported by AECL and Ontario Hydro to make them consistent with the whole body external doses calculated by the National Dosimetry Service. This was done by adding 13% to values from AECL for all years, and adding 13% to values reported by Ontario Hydro from 1982 to the present. As a result of this adjustment to preconception doses there were no changes to the number of individuals in each dose category. Accordingly, this type of measurement error could not bias the resultant odds ratios.
- (3) Historical changes to the methods of tritium dosimetry, which have resulted in a lowering of the estimated values of internal dose during more recent years, only affected doses of the fathers of controls since no case fathers had internal radiation doses. With the absence of measured doses among cases the resultant odds ratio for internal exposures could not be affected by measurement error.
- (4) The underestimation of total whole body dose for AECL workers whose dose histories were reconstructed after the AECL fire in 1956, affected six individuals in this study, all of whom were the fathers of control children. The dose for the single case father who was employed at AECL was not affected because he did not receive his first radiation exposures until the 1980's. If the true internal doses for control fathers were higher than reported in the NDR and AECL records, then the true odds ratio would be lower than that reported in Table 9.
- (5) The year of conception was prior to 1980 for all case-control sets in the Elliot Lake area. All preconception external whole body doses for uranium miners were, therefore, estimated on the basis of work history, since monitoring by badge dosimeter readings did not commence until 1981. The impact of varying the estimated dose rate for uranium miners was examined by recalculating a range of preconception doses using an arbitrarily chosen dose rate adjustment factor of two. Under the assumption that doses were under-estimated so that the true level was twice the reported value, one case and four controls shifted from the middle (0.1-49 mSv) to the upper (≥ 50 mSv) dose category, which caused the unconditional odds ratio to shift slightly from 1.3 to 1.5. Alternately, under the assumption that doses were over-estimated so that the true level was half of the reported value, both of the cases and five controls shifted from the upper (≥ 50 mSv) to the middle (0.1-49 mSv) dose category, causing the unconditional odds ratio to decline from 1.3 to 0.0.

In summary, many factors could have affected the accuracy and consistency of the radiation dose data employed in this study. Several of these factors were found to have a negligible effect on the measurement of preconception whole body dose, which was the exposure measure of primary

interest. Other factors were identified that could have appreciably affected the measured dose levels. Partly due to the fact that the largest radiation doses occurred among controls, the allocation of controls to dose categories was affected more frequently than it was for cases. Analyses of the impact of these types of measurement error indicated that when applied to cases and controls for the relevant time period or occupational group, the revised odds ratios shifted closer to 1.0. The single exception to this observation was that for uranium miners, if it was assumed that their estimated external whole body exposures were underestimated by a factor of two, then the revised odds ratio would be slightly greater than the value found in this study for the high dose category. In general, these assessments indicate that errors in the measured levels of radiation dose did not result in bias that would cause this study to fail to detect a true association between paternal radiation exposure and leukaemia in offspring.